APPENDIX 3-VII

TOXICITY PROFILES

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1 INTRODUCTION

This appendix identifies the Chemicals of Potential Concern (COPCs) and describes the acute (i.e., 10-minute, 1-hour, 8-hour and 24-hour) and chronic (i.e., annual) exposure limits used in the assessment of potential human health risks associated with the release of COPCs by the proposed MEG Energy Corp. Christina Lake Regional Project (CLRP) – Phase 3 (the Project).

2 EXPOSURE LIMIT SELECTION PROCESS

In general, chemicals can be categorized into two separate groups based on the nature of their toxic response. Threshold chemicals make up the largest category and consist of virtually all types of toxic responses and chemicals. Non-threshold chemicals are a select group of substances which potentially can produce cancer through genetically mediated mechanisms. For threshold chemicals, a minimum dose or "threshold" must be exceeded for a toxic response to be produced, and the severity or magnitude of the toxic response increases with increasing dose. Conversely, for non-threshold chemicals, regulatory policies in effect in many jurisdictions suggest that there is no safe level of exposure.

The toxicity assessment ultimately requires an understanding of the toxic effects that can be caused by the COPCs. This knowledge is typically obtained through reviewing scientific literature that describes the responses witnessed in:

- laboratory animals or human subjects following administration of the chemicals at various doses for varying periods of time under controlled conditions; and
- as part of community health studies (i.e., epidemiological investigations) examining the incidence of disease in relation to chemical exposures.

Exposure limits or "safe" levels of exposure can be derived based on the identification of a No-Observed-Adverse-Effect Level (NOAEL), which is the dose at which no adverse health effects are observed in the most sensitive species for the most sensitive health endpoint. A number of "uncertainty" or safety factors are applied to the NOAEL to provide an added level of protection, which results in an exposure limit, calculated as follows:

$$\text{Exposure Limit} = \frac{\text{NOAEL}}{\text{Uncertainty Factor(s)}}$$

Uncertainty factors can vary from 10-fold to several thousand-fold, to ensure adequate protection of any exposed population. The most common uncertainty factors applied are a 10-fold uncertainty factor to account for possible differences in sensitivity between species (i.e., interspecies differences) and a 10-fold uncertainty factor to account for differences in sensitivity between individuals of

the same species (i.e., intra-species differences). Table 1 provides a more detailed list of the most common forms of uncertainty factors.

Table 1 Commonly Used Uncertainty Factors in Determining Exposure Limits

Nature of Uncertainty	Size	Comments
Differences in sensitivity between species	3 to 10-fold	Used to accommodate the uncertainty around the use of laboratory animal data to predict potential human responses. It assumes that humans are 10 times more sensitive to the chemical than the laboratory animal.
Differences in sensitivity within a species	3 to 10-fold	Used to account for individuals within the human population that may be more sensitive to a chemical than the average person. It assumes that the sensitive individual is 10 times more responsive than the average person. This exposure limit is specific to human health assessments, as ecological assessments are concerned about the health of a population as a whole, rather than the individual.
LOAEL[(a)] to a NOAEL	3 to 10-fold	Used to account for the uncertainty surrounding the use of a LOAEL when a NOAEL is not available for the most sensitive test species. It assumes that at a dose 10 times lower than the lowest dose used in the most definitive toxicity study, no responses would be observed in the test species.
Subchronic to Chronic	3 to 10-fold	Used to account for the uncertainty surrounding the use of data involving shorter exposure periods to predict the responses that might occur over longer periods of exposure. Subchronic data is only used when exposures are expected to occur for long periods and chronic toxicity data (i.e., repeated exposures of test animals for most of their lifespan) is not available.

[(a)] The Lowest Observed Adverse Effect Level (LOAEL) refers to the lowest dose of the chemical that produces an observable adverse response in the most sensitive test species for the most sensitive health endpoint.

Uncertainty factors are required due to the practical constraints that apply to conventional toxicological research (i.e., the study of the harmful effects of chemicals). The most common research species are laboratory rodents (e.g., rats, mice, guinea pigs, rabbits), mainly because of their large numbers, low cost and the ease with which they can be housed and handled. The use of the 10-fold interspecies factor accommodates the uncertainty in extrapolating the laboratory rodent data to the human condition. It assumes that humans will be 10 times more responsive to the chemical than even the most sensitive laboratory animals. The use of the 10-fold intra-species factor recognizes the fact that the test populations of laboratory animals used in toxicity studies are specially bred to confer genetic uniformity. These animals tend to respond to chemicals in a similar manner, with only limited differences in responses between individual animals. Using the intra-species uncertainty factor respects the heterogeneity that exists among human populations and is intended to accommodate sensitive individuals who might be especially vulnerable to chemical exposures.

Exposure limits can be differentiated based on the length of exposure, recognizing the fact that the toxic response can vary for the same chemical following an acute (short-term) exposure versus a chronic (long-term) exposure. The terminology used to define exposure limits varies depending on the source of

exposure (i.e., air, water, food) and the regulatory jurisdiction involved. Generic terminology often used to describe exposure limits is as follows:

- Reference Concentration (RfC) – refers to the safe level of airborne threshold chemicals where the primary route of exposure is through inhalation. The RfC is expressed as a concentration in air (e.g., microgram per cubic metre - $\mu g/m^3$).
- Reference Dose (RfD) – refers to the safe level or dose of threshold chemicals where exposure occurs through multiple pathways, both primary and secondary (i.e., oral, dermal). The RfD is commonly expressed as the dose of the chemical per unit body weight of the receptor per day (e.g., microgram per kilogram of body weight per day - µg/kg bw/d).
- Risk-specific Concentration (RsC) – reserved for non-threshold carcinogens, the RsC refers to the concentration via inhalation that corresponds to a regulatory acceptable incremental increase in the incidence of cancer, typically of one in 100,000. The RsC is expressed as a concentration in air (e.g., $\mu g/m^3$).
- Risk-specific Dose (RsD) – same as the RsC except that it refers to the dose from multiple pathways that corresponds to a regulatory acceptable incremental increase in the incidence of cancer (one in 100,000), often expressed as the dose of the chemical per unit body weight of the receptor per day (e.g., µg/kg bw/d).

In some instances, reliance must be placed on a guiding principle which states that the molecular structure of a chemical has a distinct bearing on its reactivity, biological activity and toxicity. This principle allows the toxicity of a chemical for which little or no toxicological information exists to be predicted on the basis of information available on another chemical of similar molecular structure. The second chemical is often termed a "surrogate" and the term "read across" has been coined to describe the principle. The principle is also often applied to groups of chemicals of similar structure in which toxicity data on many of the individual constituents of the group may be lacking. In such cases, all of the constituents are assumed to share the same toxic potency as the most toxic chemical in the group for which toxicity information is known.

Exposure to chemicals typically does not occur in isolation; thus, consideration was given to the potential health effects associated with chemical mixtures. The interaction between chemicals can take many forms, depending on the chemicals present, their mode of action and their concentrations. Common forms of interaction include additivity, synergism, antagonism and potentiation. Of these four, additivity is the most plausible form of interaction. Additive chemicals are structurally similar, act toxicologically via similar mechanisms or affect the same

target tissue in the body. For instance, chemicals that result in respiratory irritant effects will often be added together. As per Health Canada's (2004a) guidance, chemical interactions were assumed to be additive in nature.

Chemicals of potential concern were assessed on an individual basis if a standard, guideline or objective was available from a regulatory agency or leading scientific authority that is protective of air quality and human health. Selection of each exposure limit required that the limit be:

- protective of the health of the general public based on the current scientific understanding of the health effects known to be associated with exposures to the COPC;
- protective of sensitive individuals, including children and the elderly, through the use of safety or uncertainty factors;
- established or recommended by reputable scientific authorities; and
- supported by adequate documentation.

If the above criteria were supported by more than one standard, guideline or objective, the most stringent exposure limit was selected. Otherwise, the rationale for selection of an alternative exposure limit is provided.

2.1 SELECTION OF ACUTE EXPOSURE LIMITS

On an acute basis, the sources of exposure limits used in the Human Health Risk Assessment (HHRA) include:

- the Ambient Air Quality Objectives (AAQOs) developed by Alberta Environment (AENV 2007, Website);
- the acute Minimum Risk Levels (MRLs) developed by the Agency for Toxic Substances and Disease Registry (ATSDR 2006a);
- the acute Reference Exposure Levels (RELs) developed by the California Office of Environmental Health Hazard Assessment (OEHHA 2007a);
- the Ambient Air Quality Criteria (AAQCs), Standards and Point of Impingement Guidelines (POIs) developed by the Ontario Ministry of the Environment (OMOE 2005a); and
- the Air Quality Guidelines for Europe (Second Edition) developed by the World Health Organization (WHO 2000, Website).

If a suitable exposure limit could not be identified by one of the above regulatory agencies, then the search was expanded to include:

- the intermediate MRLs developed by the Agency for Toxic Substances and Disease Registry (ATSDR 2006a); and
- the short-term Threshold Limit Values (e.g., TLV ceiling) or Short-Term Exposure Limits (STELs) developed by the American Conference of Governmental Industrial Hygienists (ACGIH 2006a).

Oral exposure limits, even if obtained from a short-term study, were not used in the derivation of any acute inhalation limits because:

- the target tissues of the critical effects associated with acute inhalation are often at the portal of entry (i.e., respiratory system);
- differences in absorption between the respiratory system and the digestive system; and
- oral exposure limits can be based on repeated dosing via the oral route of exposure (i.e., gavage, ingestion).

2.2 SELECTION OF CHRONIC EXPOSURE LIMITS

The sources of exposure limits used in the HHRA for the chronic toxicity assessment include the regulatory agencies outlined by Health Canada (2004a) in the "Federal Contaminated Site Risk Assessment in Canada":

- the chronic MRLs developed by the Agency for Toxic Substances and Disease Registry (ATSDR 2006a);
- the Toxicological Reference Values (TRVs) developed by Health Canada (2004b,c);
- the Maximum Permissible Risk Levels developed by the Netherlands National Institute of Public Health and the Environment (RIVM 2001);
- the Integrated Risk Information System (IRIS) provided by the United States Environmental Protection Agency (U.S. EPA 2007, Website); and
- the Air Quality Guidelines for Europe (Second Edition) developed by the World Health Organization (WHO 2000, Website).

Once again, if a suitable exposure limit was not available from one of the above regulatory agencies, the search was expanded to include:

- the chronic RELs developed by the California Office of Environmental Health Hazard Assessment (OEHHA 2007b); and
- the time-weighted average TLVs developed by the American Conference of Governmental Industrial Hygienists (ACGIH 2006a).

3 EXPOSURE LIMITS FOR THE CHEMICALS OF POTENTIAL CONCERN

3.1 ALIPHATIC C_2-C_8 GROUP

3.1.1 Acute Exposure Limit

Table 2 shows the acute exposure limits for the aliphatic C_2-C_8 group as defined by the regulatory agencies.

Table 2 Acute Inhalation Exposure Limits for the Aliphatic C_2-C_8 Group

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	—	—	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	—	—	OEHHA (2007a)
OMOE	2,500[(a)]	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

[(a)] The OMOE standard was developed for an n-hexane mixture (OMOE 2005b).

— = Not available.

The OMOE provides a 24-hour standard of 2,500 µg/m^3 for an n-hexane mixture (OMOE 2005a,b). This standard was developed from a NOAEL of 58 ppm (204 mg/m^3) for polyneuropathy in humans (Sanagi et al. 1980). Workers were exposed to low concentrations of n-hexane and acetone in a tungsten carbide alloys facility for an average of 6.2 years. Significant decreases in mean motor nerve conduction velocities and slowed residual latency of motor conduction of lower extremities were observed. The NOAEL was adjusted from an eight-hour time weighted average for occupational exposure to a value of 73 mg/m^3 for continuous exposure in the general population as follows:

$$NOAEL_{ADJ} = NOAEL \times \frac{MV_{ho}}{MV_h} \times \frac{Exp_{ho}}{Exp_h}$$

Where:

$NOAEL_{ADJ}$ = NOAEL in the human population from continuous exposure (mg/m^3)

NOAEL = NOAEL for discontinuous exposure in an occupational setting (204 mg/m^3)

MV_{ho} = amount of air used by a worker during an 8-hour work period (10 m^3/d)

MV_h = amount of air used by an individual in the general population during a day (20 m^3/d)

Exp_{ho} = days per week a worker is exposed (5 days)

Exp_h = days per week an individual in the general population is exposed (7 days)

The OMOE (2005b) applied an uncertainty factor of 30 to the $NOAEL_{ADJ}$ to account for individual sensitivity (10-fold) and potential interaction with other hydrocarbon solvents in commercial n-hexane (3-fold). The study team does not support the use of chronic toxicity data in the derivation of an acute limit. Thus, an alternate acute guideline with supporting documentation was identified for the aliphatic C_2-C_8 group.

The Canadian Council of Ministers of the Environment (CCME 2000a) and the Total Petroleum Hydrocarbon Criteria Working Group (TPHCWG 1997) have developed a chronic RfC for C_2-C_8 aliphatics based on a NOAEL of 3,000 ppm (10,000 mg/m^3) identified in four subchronic and chronic studies. The NOAELs identified from the subchronic studies are based on increased liver weights in rats and mice and nephropathy in rats exposed to 0, 900, 3,000 or 9,000 ppm (0, 3,000, 10,000, 30,000 mg/m^3) commercial hexane for six hours per day, five days per week for 13 weeks (Duffy et al. 1991). An uncertainty factor of 100 was applied to the subchronic NOAEL of 3,000 ppm (10,000 mg/m^3) to account for interspecies variability (10-fold) and intra-species variability (10-fold). Because the C_2-C_8 aliphatic group includes a variety of organic compounds with 2 to 8 carbon atoms joined together in a straight or branched chain and is not limited to n-hexane and its isomers. The limit of 100,000 µg/m^3 was used as a 1-hour exposure limit in the acute effects assessment of the aliphatic C_2-C_8 group.

Use of a subchronic NOAEL in the derivation of an acute exposure limit is considered conservative since a higher exposure over a shorter period (i.e., acute exposure) presumably could occur without risk of adverse effects.

3.1.2 Chronic Exposure Limit(s)

In the case of the aliphatic and aromatic Petroleum Hydrocarbon (PHC) groups, the search for chronic inhalation and oral exposure limits was limited to three regulatory agencies that have developed chronic exposure limits that are representative of the aliphatic and aromatic groups as a whole: CCME (2000a), Massachusetts Department of Environmental Protection (MA DEP 2003) and TPHCWG (1997) (Table 3).

Table 3 Chronic Inhalation Exposure Limits for the Aliphatic C_2-C_8 Group

Regulatory Agency	Value [µg/m^3]	Type	Source
CCME	18,400	RfC	CCME (2000a)
MA DEP	200	RfC	MA DEP (2003)
TPHCWG	18,400	RfC	TPHCWG (1997)

The CCME (2000a) provides an RfC of 18,400 µg/m^3 for the C_2-C_8 aliphatic group based on the neurotoxic endpoint of commercial hexane. This exposure limit was adopted from the TPHCWG (1997) and was developed from the NOAEL of 10,307 mg/m^3 for two (rat and mice) chronic bioassays involving lifetime exposure. The NOAEL was adjusted for continuous exposure (6 hours/24 hours x 5 days/7 days) to a concentration of 1,840 mg/m^3. The TPHCWG (1997) applied an uncertainty factor of 100 to account for interspecies variability (10-fold) and intra-species variability (10-fold).

The TPHCWG (1997) recommends using the RfC derived for commercial hexane over an RfC specific to n-hexane (as is the case of the MA DEP RfC) as it is more representative of the aliphatic fraction. According to the TPHCWG (1997), using n-hexane alone results in an overestimation of the toxicity of the fraction because n-hexane is the most toxic of the group's constituents, it is uniquely toxic and its interaction with other petroleum compounds influences its toxicity. On this basis, the RfC of 18,400 µg/m^3 for commercial hexane was used to evaluate the risks associated with this petroleum mixture. This RfC corresponds to an inhalation dose of 4,100 µg/kg bw/d based on an average adult body weight of 70.7 kg and an inhalation rate of 15.8 m^3/d (Health Canada 2004a).

The MA DEP (2003) RfC of 200 µg/m^3 was developed from toxicity data specific to n-hexane, which is considered overly conservative and inappropriate when characterizing the toxicity of the aliphatic C_2-C_8 group as a whole. Furthermore, the MA DEP (2003) adopted the 1993 U.S. EPA RfC for n-hexane, which was increased in 2005 to a value of 700 µg/m^3 for peripheral neuropathy in a subchronic rat inhalation study (U.S. EPA 2005a, Website).

The aliphatic C_2-C_8 group was identified as a potentially persistent and bioaccumulative chemical in the environmental media. Therefore, it was assessed via multiple exposure pathways and required an oral exposure limit (Table 4).

Table 4 Chronic Oral Exposure Limits for the Aliphatic C_2-C_8 Group

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
CCME	5,000	RfD	CCME (2000a)
MA DEP	40	RfD	MA DEP (2003)
TPHCWG	5,000	RfD	TPHCWG (1997)

The CCME (2000a) provides an RfD of 5,000 µg/kg bw/d based on the neurotoxicity of commercial hexane. As in the chronic inhalation assessment, this RfD was adopted from the TPHCWG (1997). The TPHCWG (1997) developed the oral RfD from the inhalation limit (discussed above), assuming an adult body weight of 70 kg, a breathing rate of 20 m^3/d and 100% absorption.

The MA DEP (2003) recommends an oral RfD of 40 µg/kg bw/d based on reduced body weight and neurotoxicity. In a subchronic gavage study, a LOAEL of 570 mg/kg bw/d was identified in rats exposed to n-hexane. The LOAEL was adjusted for discontinuous exposure (5 days/7 days) to a concentration of 407 mg/kg bw/d (MA DEP 2003). The MA DEP (2003) applied an uncertainty factor of 10,000 to the duration-adjusted LOAEL to account for interspecies variability (10-fold), intra-species variability (10-fold), subchronic to chronic extrapolation (10-fold) and use of a LOAEL (10-fold). As in the chronic inhalation assessment (discussed above), use of an RfD developed on the basis of n-hexane toxicity alone is overly conservative and inappropriate when characterizing the toxicity of the aliphatic C_2-C_8 group as a whole. In addition, the degree of uncertainty identified by the MA DEP (2003) with the application of a 10,000-fold uncertainty factor does not imply a high degree of confidence in the limit. Thus, the CCME RfD of 5,000 µg/kg bw/d was selected as the chronic oral exposure limit for this aliphatic group.

For incorporation in the multiple pathway exposure assessment, inhalation bioavailability was assumed to be 100% (no specific data were identified in the literature regarding the amount of C_2-C_8 aliphatic that is absorbed via inhalation). As well, an oral bioavailability in humans of 80% and a dermal bioavailability of 1% were assumed based on n-hexane (RAIS 2007, Website).

3.2 ALIPHATIC C_9-C_{16} GROUP

3.2.1 Acute Exposure Limit

After reviewing available information and determining that an acute inhalation limit was not available for this group of compounds, an acute inhalation exposure

limit was developed from the subchronic LOAEL that formed the basis of the MA DEP's (2003) chronic RfC.

The MA DEP (2003) has developed a chronic RfC for the aliphatic C_9-C_{16} group from a subchronic inhalation study (Lund et al. 1995). Sprague-Dawley rats were exposed to 0, 2,600 or 5,300 mg/m^3 (0, 400 or 800 ppm) of de-aromatized white spirit vapours (DAWS) for six hours per day, five days per week for six months. Following a two to six month exposure-free period, neurophysiological, neurobehavioural and microscopic pathologic examinations were performed. Exposure-related changes in sensory evoked potentials were observed and a decrease in motor activity during dark periods was reported. According to the authors, a six month exposure to DAWS can result in long-lasting and possibly irreversible effects in the nervous system of the rat.

In the derivation of the acute inhalation limit, an uncertainty factor of 1,000 was applied to the LOAEL of 2,600 mg/m^3 to account for interspecies variability (10-fold), intra-species variability (10-fold) and adjusting from a LOAEL to a NOAEL (10-fold). The limit of 2,600 µg/m^3 was used as a 1-hour exposure limit for the acute effects assessment of the aliphatic C_9-C_{16} group.

Use of a subchronic LOAEL in the derivation of an acute exposure limit is considered conservative since a higher exposure over a shorter time-period (i.e., acute exposure) presumably could occur without risk of adverse effects.

3.2.2 Chronic Exposure Limit(s)

In the case of the aliphatic and aromatic PHC groups, the search for chronic inhalation and oral exposure limits was limited to three regulatory agencies that have developed chronic exposure limits that are representative of the aliphatic and aromatic groups as a whole: CCME (2000a), MA DEP (2003) and TPHCWG (1997) (Table 5).

Table 5 Chronic Inhalation Exposure Limits for the Aliphatic C_9-C_{16} Group

Regulatory Agency	Value [µg/m^3]	Type	Source
CCME	1,000	RfC	CCME (2000a)
MA DEP	200	RfC	MA DEP (2003)
TPHCWG	1,000	RfC	TPHCWG (1997)

The CCME (2000a) provides an RfC of 1,000 µg/m^3 for the aliphatic C_9-C_{16} group, which was adopted from the TPHCWG (1997). The RfC is based on the

hepatic and haematological effects of de-aromatized petroleum streams and JP-8 Jet Fuel, which together cover the entire range of the fraction. Two separate studies were examined by the TPHCWG (1997):

- Study #1 (Phillips and Egan 1984): Sprague-Dawley rats were exposed to 0, 300 or 900 ppm of C_{10}-C_{11} isoparaffinic solvent for six hours per day, five days per week for 12 weeks. The NOAEL of 900 ppm (5,226 mg/m^3) was adjusted for intermittent exposure (6 hours/24 hours x 5 days/7 days) to a concentration of 933 mg/m^3. An uncertainty factor of 1,000 was applied to the duration-adjusted NOAEL to account for interspecies variability (10-fold), intra-species variability (10-fold) and use of a subchronic study (10-fold). The result is an RfC of 0.9 mg/m^3.
- In the same study, Sprague-Dawley rats were exposed to 0, 300 or 900 ppm of de-aromatized white spirit vapours (DAWS) for six hours per day, five days per week for 12 weeks. The study NOAEL of 5,485 mg/m^3 was adjusted for intermittent exposure (6 hours/24 hours x 5 days/7 days) to a concentration of 979 mg/m^3. An uncertainty factor of 1,000 was applied to the adjusted NOAEL to account for interspecies variability (10-fold), intra-species variability (10-fold) and use of a subchronic study (10-fold). The result is an RfC of 1.0 mg/m^3.
- Study #2 (Mattie et al. 1991): Mice and rats were exposed to JP-8 vapours continually for 90 days. A NOAEL of 1,000 mg/m^3 was identified and an uncertainty factor of 1,000 was applied to account for interspecies variability (10-fold), intra-species variability (10-fold) and use of a subchronic study (10-fold). The result is an RfC of 1.0 mg/m^3.

Based on these two studies (RfCs range between 0.9 and 1.0 mg/m^3), an RfC of 1,000 µg/m^3 was selected by the TPHCWG (1997).

In contrast, the MA DEP (2003) examined the two following studies:

- Study #1 (Phillips and Egan 1984): The MA DEP identified the same key study as the TPHCWG; however, the concentration the TPHCWG identified as a NOAEL was reported as a LOAEL by the MA DEP. As a result, the MA DEP applied an additional uncertainty factor of 3 in the derivation of the RfC to account for the use of a LOAEL, resulting in an RfC of 0.3 mg/m^3, instead of 0.9 or 1.0 mg/m^3.
- Study #2 (Lund et al. 1995): The MA DEP considered a subchronic inhalation study that exposed rats to 0, 2,620 or 5,253 mg/m^3 (0, 400 or 800 ppm) of DAWS for six hours per day, five days per week for six months. Following a two to six month exposure-free period, neurophysiological, neurobehavioural and microscopic pathologic examinations were performed. Exposure-related changes in sensory evoked potentials were observed and a decrease in motor activity during

dark periods was reported. According to the authors, a six-month exposure to DAWS can result in long-lasting and possibly irreversible effects in the nervous system of the rat. The LOAEL of 2,620 mg/m^3 (400 ppm) was adjusted for continuous exposure (6 hours/24 hours x 5 days/7 days) to a concentration of 468 mg/m^3. An uncertainty factor of 3,000 was applied by the MA DEP to account for interspecies variability (10-fold), intra-species variability (10-fold), adjusting from a LOAEL to a NOAEL (10-fold) and use of a subchronic study (3-fold). The result is an RfC of 0.2 mg/m^3.

Based on these two studies the MA DEP (2003) established an RfC of 200 µg/m^3 for neurotoxicity.

Upon review of the Phillips and Egan (1984) study, the study team concluded that the MA DEP accurately interpreted the exposure concentration of 300 ppm as a LOAEL and not a NOAEL as the TPHCWG and CCME reported. Phillips and Egan (1984) observed increase kidney weights and alterations in kidney structure in male rats in the low and high exposure groups for both the C_{10}-C_{11} isoparaffinic solvent- and DAWS-exposed male rats. The effect appeared to be dose related and time dependant (Phillips and Egan 1984). As a result, the MA DEP (2003) RfC of 200 µg/m^3 was selected for the chronic inhalation effects assessment of the aliphatic C_9-C_{16} group. This RfC corresponds to an inhalation dose of 45 µg/kg bw/d based on an average adult body weight of 70.7 kg and an inhalation rate of 15.8 m^3/d (Health Canada 2004a).

The aliphatic C_9-C_{16} group was identified as a potentially persistent and bioaccumulative chemical in the environmental media. Therefore, it was assessed via multiple exposure pathways and required an oral exposure limit (Table 6).

Table 6 Chronic Oral Exposure Limits for the Aliphatic C_9-C_{16} Group

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
CCME	100	RfD	CCME (2000a)
MA DEP	100	RfD	MA DEP (2003)
TPHCWG	100	RfD	TPHCWG (1997)

An RfD of 100 µg/kg bw/d is provided by the CCME (2000a) for the aliphatic C_9-C_{16} group, which was adopted from the TPHCWG (1997). The RfD is based on hepatic and haematological effects in rats exposed to de-aromatized C_9-C_{13} aliphatics (TPHCWG 1997). Two separate studies were examined by the TPHCWG:

- Study #1: Rats were dosed orally with C_9-C_{12} aliphatics including isoparaffins, naphthenes and n-alkanes for 90 days. A LOAEL of 500 mg/kg bw/d was identified based on observed reversible liver and haematological effects. An uncertainty factor of 5,000 was applied to the study LOAEL to account for interspecies variability (10-fold), intra-species variability (10-fold), use of a subchronic study (10-fold) and use of a LOAEL versus a NOAEL (5-fold). The result is an RfD of 0.1 mg/kg bw/d.
- Study #2: Rats were exposed to C_{10}-C_{13} aliphatics including isoparaffins, naphthenes and n alkanes for 13 weeks. A NOAEL of 100 mg/kg bw/d was identified. The TPHCWG (1997) applied an uncertainty factor of 1,000 to the study NOAEL to account for intra-species variation (10-fold), interspecies variation (10-fold) and use of a subchronic study (10-fold). The result is an RfD of 0.1 mg/kg bw/d.

An RfD of 0.1 mg/kg bw/d was selected from the aforementioned studies by the TPHCWG (1997). In addition to the above studies, the TPHCWG considered toxicity data for JP-8 Jet Fuel and C_{11}-C_{17} isoparaffinic solvent, which were less conservative.

Similar to the TPHCWG, the MA DEP (2003) RfD of 100 µg/kg bw/d was developed from three separate studies:

- Study #1 (Anon 1991a): Rats were orally dosed with 0, 500, 2,500 or 5,000 mg/kg bw/d of C_9-C_{12} isoparaffins, n-alkanes and naphthalenes for 90 days. A LOAEL of 500 mg/kg bw/d was identified for changes in serum chemistry and liver weight. An uncertainty factor of 5,000 was applied to the LOAEL to account for interspecies variability (10-fold), intra-species variability (10-fold), use of a subchronic study (10-fold) and use of a LOAEL (5-fold). The result is an RfD of 0.1 mg/kg bw/d.
- Study #2 (Anon 1991b): Rats were orally treated with 0, 100, 500 or 1,000 mg/kg bw/d of C_{10}-C_{13} isoparaffins, n-alkanes and naphthalenes for 13 weeks. A NOAEL of 100 mg/kg bw/d was identified for changes in serum chemistry and liver weight. An uncertainty factor of 1,000 was applied to the adjusted NOAEL to account for interspecies variability (10-fold), intra-species variability (10-fold) and use of a subchronic study (10-fold). The result is an RfD of 0.1 mg/kg bw/d.

- Study #3 (Anon 1990): Rats were orally treated with 0, 100, 500 or 1,000 mg/kg bw/d of C_{11}-C_{17} isoparaffinic solvent for 13 weeks. A NOAEL of 100 mg/kg bw/d was identified based on observed liver effects. An uncertainty factor of 1,000 was applied to the adjusted NOAEL to account for interspecies variability (10-fold), intra-species variability (10-fold) and use of a subchronic study (10-fold). The result is an RfD of 0.1 mg/kg bw/d.

As in the TPHCWG (1997) assessment, an RfD of 0.1 mg/kg bw/d was selected from the above studies by the MA DEP (2003). Thus, an RfD of 100 µg/kg bw/d was used in the chronic oral effects assessment for the aliphatic C_9-C_{16} group.

For incorporation in the multiple pathway exposure assessment, inhalation, oral and dermal bioavailability was assumed to be 100% since no data were identified in the literature regarding the amount of aliphatic C_9-C_{16} or any of the individual constituents that is absorbed via inhalation.

3.3 ALIPHATIC C_{17}-C_{34} GROUP

3.3.1 Acute Exposure Limit

As no defensible acute exposure limits were identified for this group, an acute effects assessment was not completed for the aliphatic C_{17}-C_{34} group. As a result, the aliphatic C_{17}-C_{34} group was assessed on a chronic basis only.

3.3.2 Chronic Exposure Limit(s)

In the case of the aliphatic and aromatic PHC groups, the search for chronic inhalation and oral exposure limits was limited to three regulatory agencies that have developed chronic exposure limits that are representative of the aliphatic and aromatic groups as a whole: CCME (2000a), MA DEP (2003) and TPHCWG (1997).

According to the CCME (2000a), appropriate inhalation toxicity data were not identified for the individual constituents or fractions in the C_{17}-C_{34} carbon range. The CCME (2000a) suggests that this could be the result of the hydrocarbons in this group not being volatile and inhalation not being the likely exposure pathway. The MA DEP does not provide an RfC for exposure to C_{19}-C_{32} aliphatics either. The MA DEP (2003) attributes this to the limited volatility of the group. Nevertheless, the C_{17}-C_{34} aliphatics will be emitted to the atmosphere from the proposed Project and thus requires an inhalation limit. Given that a chronic inhalation limit is not provided by CCME (2000a), MA DEP (2003) or

TPHCWG (1997), the toxicity search was expanded to include the chronic oral criteria or guidelines provided by any of these regulatory agencies (Table 7).

Table 7 Chronic Oral Exposure Limits for the Aliphatic C_{17}-C_{34} Group

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
CCME	2,000	RfD	CCME (2000a)
MA DEP	2,000	RfD	MA DEP (2003)
TPHCWG	2,000	RfD	TPHCWG (1997)

The CCME (2000a) and the TPHCWG (1997) provide an oral RfD of 2,000 µg/kg bw/d based on liver granulomas in rats. F/344 rats were administered a range of white mineral oils in the diet at doses of 2, 200, 2,000 and 20,000 ppm (2, 20, 200 and 2,000 mg/kg/d) for 90 days (Smith et al. 1996). Liver granulomas were observed in rats administered the low molecular weight mineral oils (C_{17}-C_{34}) at 2,000 mg/kg/d. No effects were observed in the rats administered the high molecular weight mineral oils with chains containing greater than 34 carbon atoms ($C_{>34}$). A NOAEL of 200 mg/kg/d was identified for the low molecular weight oils and a NOAEL of 2,000 mg/kg/d was identified in the high molecular weight oils. The TPHCWG (1997) applied an uncertainty factor of 100 to the NOAEL of 200 mg/kg/d for the low molecular weight oils to account for interspecies variability (3-fold), intra-species variability (10-fold) and subchronic to chronic extrapolation (3-fold). An uncertainty factor of 3 was used for animal to human extrapolation because human exposure to natural dietary oils and mineral hydrocarbons have not shown any clinical effects. F/344 rats also appear to be a sensitive species and predisposed to granulomatous effects (lesions or localized inflammation found in tissues), as similar doses administered to dogs, mice and other strains of rats have not produced these effects. Further, the granulomatous responses do not appear to progress to tumours or alter lifetime, body weight or health status of rats (TPHCWG 1997).

The MA DEP (2003) originally provided an oral RfD of 600 µg/kg bw/d derived from a lifetime dietary feeding study of white mineral oils in rats. However, the MA DEP (2003) has chosen to adopt the TPHCWG's oral RfD because the study used a full range of refined mineral oils, the effects of the mineral oils were inversely related to molecular weight and the lack of effect with the higher molecular weight oils is consistent with studies showing no absorption for alkanes above C_{32}.

The TPHCWG (1997) oral RfD of 2,000 µg/kg bw/d was converted to an inhalation limit of 8,950 µg/m^3 based on the following adjustments and assumptions:

- inhalation bioavalability and oral bioavailability of 100% (assumed);
- adult body weight of 70.7 kg (Health Canada 2004a); and
- adult inhalation rate of 15.8 m^3/d (Health Canada 2004a).

The aliphatic C_{17}-C_{34} group was identified as a potentially persistent and bioaccumulative chemical in the environmental media. Therefore, it was assessed via multiple exposure pathways and required an oral exposure limit. The oral RfD of 2,000 µg/kg bw/d was used in the chronic effects assessment of the aliphatic C_{17}-C_{34} group.

As no data were identified in the literature regarding the absorption of aromatic C_{17}-C_{34} group or any of the individual constituents, oral and dermal bioavailability were also assumed to be 100% in the multiple pathway exposure assessment.

3.4 AROMATIC C_9-C_{16} GROUP

3.4.1 Acute Exposure Limit

After reviewing available information and determining that an acute inhalation limit was not available for this group of compounds, an acute inhalation exposure limit was developed from the subchronic NOAEL that formed the basis of the CCME's chronic RfC.

The CCME (2000a) and TPHCWG (1997) developed a chronic RfC for the aliphatic C_9-C_{16} group from a subchronic inhalation study. Rats were exposed to a mixture of C_9 aromatics (High Flash Aromatic Naphtha [HFAN]) at concentrations of 0, 450, 900 or 1,800 mg/m^3 for six hours per day, five days per week for 12 months (Clark et al. 1989). Increased liver and kidney weights were reported for male rats in the 1,800 mg/m^3 exposure group. The MA DEP (2003) also reviewed the Clark et al. study and, in addition to liver toxicity, identified Central Nervous System (CNS) effects associated with the LOAEL of 1,800 mg/m^3.

In the derivation of the acute inhalation exposure limit, an uncertainty factor of 100 was applied to the NOAEL of 900 mg/m^3 to account for the interspecies variability (10-fold) and intra-species variability (10-fold). The result is a

modified acute inhalation exposure limit of 9,000 µg/m^3. This limit was used as a 1-hour exposure limit in the acute effects assessment of the aromatic C_9-C_{16} group.

Use of a subchronic study in the derivation of an acute exposure limit is considered conservative since a higher exposure over a shorter time-period (i.e., acute exposure) presumably could occur without risk of adverse effects.

3.4.2 Chronic Exposure Limit(s)

In the case of the aliphatic and aromatic PHC groups, the search for chronic inhalation and oral exposure limits was limited to three regulatory agencies that have developed chronic exposure limits that are representative of the aliphatic and aromatic groups as a whole: CCME (2000a), MA DEP (2003) and TPHCWG (1997) (Table 8).

Table 8 Chronic Inhalation Exposure Limits for the Aromatic C_9-C_{16} Group

Regulatory Agency	Value [µg/m^3]	Type	Source
CCME	200	RfC	CCME (2000a)
MA DEP	50	RfC	MA DEP (2003)
TPHCWG	200	RfC	TPHCWG (1997)

The CCME (2000a) provides a chronic RfC for C_9-C_{16} aromatics of 200 µg/m^3 which was adopted from the TPHCWG (1997). The chronic RfC is based on increased liver and kidney weights in male rats exposed to High Flash Aromatic Naphtha (HFAN), which is primarily composed of 9-carbon aromatic compounds. Rats were administered 0, 450, 900 or 1,800 mg/m^3 of a mixture of C_9 aromatics for six hours per day, five days per week for 12 months (Clark et al. 1989). A NOAEL of 900 mg/m^3 was identified for liver and kidney effects and converted to continuous exposure (6 hours/24 hours x 5 days/7 days). The TPHCWG (1997) applied an uncertainty factor of 1,000 to the duration-adjusted NOAEL of 160 mg/m^3 to account for the interspecies variability (10-fold), intra-species variability (10-fold) and use of a subchronic study (10-fold).

The MA DEP (2003) provides an RfC of 50 µg/m^3 based on the same Clark et al. (1989) study as the TPHCWG and the CCME. However, the MA DEP (2003) identifies CNS effects as one of the key endpoints (in addition to liver effects) and applies an extra 3-fold uncertainty factor to account for database deficiency. This partial uncertainty factor was applied to account for the lack of toxicity

information on non-Polycyclic Aromatic Hydrocarbons (PAH) compounds in the C_9-C_{16} aromatic fraction range (MA DEP 2003).

For the purpose of assessing chronic inhalation effects, the TPHCWG (1997) and the CCME (2000a) both consider there to be an adequate database for the derivation of an RfC that is representative of the C_9-C_{16} aromatics. As a result, the CCME RfC of 200 µg/m^3 was used in the chronic inhalation effects assessment. This RfC equates to an inhaled dose of 45 µg/kg bw/d based on an average adult body weight of 70.7 kg and an inhalation rate of 15.8 m^3/d (Health Canada 2004a).

The aromatic C_9-C_{16} group was identified as a potentially persistent and bioaccumulative chemical in the environmental media. Therefore, it was assessed via multiple exposure pathways and required an oral exposure limit (Table 9).

Table 9 Chronic Oral Exposure Limits for the Aromatic C_9-C_{16} Group

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
CCME	40	RfD	CCME (2000a)
MA DEP	30	RfD	MA DEP (2003)
TPHCWG	40	RfD	TPHCWG (1997)

The CCME (2000a) recommends an oral RfD of 40 µg/kg bw/d for the C_9-C_{16} aromatics based on the most commonly reported RfD value of eight individual compounds for which the U.S. EPA has established oral RfDs (isopropylbenzene, acenaphthene, biphenyl, fluorene, anthracene, fluoranthene, naphthalene, pyrene). The CCME adopted this value from the TPHCWG (1997), who examined the aforementioned RfDs for liver and kidney effects together with toxicity data for naphthalenes/methylnaphthalenes to determine the RfD of 0.04 mg/kg bw/d. At the time of the TPHCWG (1997) assessment, four of the eight individual compounds (isopropylbenzene, naphthalene, fluorene and fluoranthene) had RfDs of 0.04 mg/kg bw/d, while the remaining compounds had RfDs ranging from 0.03 mg/kg bw/d to 0.3 mg/kg bw/d.

Alternatively, the MA DEP (2003) selected the U.S. EPA RfD for pyrene of 0.03 mg/kg bw/d to represent the entire range of compounds. The U.S. EPA RfD for pyrene is based on kidney effects (renal tubular pathology, decreased kidney weights) observed in a subchronic mouse oral bioassay. This value has not been updated since the MA DEP assessment (U.S. EPA 1993a, Website).

Although the U.S. EPA has revised the isopropylbenzene (0.1 mg/kg bw/d) and naphthalene (0.02 mg/kg bw/d) RfDs since the TPHCWG's assessment (U.S. EPA 1997, Website; 1998a, Website), it is important that the RfD of the group reflect the toxicity of the group as a whole and not a single compound within the group. On this basis, the CCME (2000a) oral RfD of 40 µg/kg bw/d was used in the chronic oral effects assessment of the C_9-C_{16} aromatics.

To incorporate the aromatic C_9-C_{16} group in the multiple pathway exposure assessment, bioavailability was assessed via a surrogate (naphthalene) for the various exposure pathways (i.e., inhalation, ingestion and dermal contact). No specific data were identified in the literature regarding the amount of the aromatic C_9-C_{16} group that is absorbed via inhalation; therefore it was conservatively assumed that 100% of the inhaled group is absorbed. Oral bioavailability in humans was assumed to be 80% and dermal bioavailability was assumed to be 13% for this assessment (RAIS 2007, Website).

3.5 AROMATIC C_{17}-C_{34} GROUP

3.5.1 Acute Exposure Limit

After reviewing available information and determining that an acute inhalation limit is not available for this group of compounds, an acute inhalation limit was developed from the subchronic oral NOAEL that formed the basis of the CCME's chronic RfD.

The CCME (2000a) and TPHCWG (1997) identified pyrene as a surrogate for the fraction because it has a lower carbon number than any of the compounds in this fraction. Both regulatory agencies adopted the U.S. EPA RfD as its RfD. The U.S. EPA identified a NOAEL of 75 mg/kg bw/d for kidney effects (renal tubular pathology, decreased kidney weights) in a mouse subchronic oral bioassay (TPHCWG 1997). Male and female CD-1 mice (20/sex/group) were gavaged with 0, 75, 125, or 250 mg/kg bw/d pyrene in corn oil for 13 weeks. Due to the subchronic study design, the nature of the adverse effects observed and the potential uncertainties associated with route-route extrapolation on an acute basis, this limit was not appropriate for use in association with acute exposures. As no defensible acute exposure limit was identified for the aromatic C_{17}-C_{34} fraction, this COPC group was not evaluated on an acute basis.

3.5.2 Chronic Exposure Limit(s)

Appropriate inhalation toxicity data were not identified for the individual constituents or fractions in the C_{17}-C_{34} carbon range (CCME 2000a). This could

be the result of the hydrocarbons in this group not being volatile and inhalation not being the likely exposure pathway. In addition, Massachusetts Department of Environmental Protection (MA DEP 2003) does not provide a recommended value for inhalation exposure to C_{19}-C_{32} aromatics based on the limited volatility of the group. Nevertheless, the C_{17}–C_{34} aromatics will be emitted to the atmosphere from the proposed facility and thus require an inhalation limit.

The oral RfD provided by Canadian Council of Ministers of the Environment (CCME 2000a) was converted to a RfC of 130 µg/m^3 based on the following adjustments and assumptions:

- inhalation bioavailability and oral bioavailability of 100% (assumed);
- adult body weight of 70.7 kg; and
- adult inhalation rate of 15.8 m^3/day (Health Canada 2004a).

The CCME (2000a) recommends an oral RfD of 30 µg/kg bw/d for the aromatic C_{17}-C_{34} fraction. This RfD was adopted from the TPHCWG (1997) and is based on the nephrotoxicity of pyrene. No previously developed RfDs or appropriate data exist for compounds within the C_{17}-C_{34} fraction. The RfD for pyrene was derived from a NOAEL of 75 mg/kg bw/d with an uncertainty factor of 1,000 applied to the NOAEL to account for interspecies variability (10-fold), intra-species variability (10-fold) and using a subchronic study (10-fold). A modifying factor of 3 was also applied to the RfD because of the lack of adequate toxicity data. This RfD of 30 µg/kg bw/d was used in the chronic oral effects assessment of the C_{17}-C_{34} aromatics.

For incorporation in the multiple exposure pathway model, inhalation, oral and dermal bioavailability was assumed to be 100% as no data were identified in the literature regarding the amount of aromatic C_{17}-C_{34} or any of the individual constituents absorbed via inhalation, oral or dermal exposure.

3.6 ARSENIC

3.6.1 Acute Exposure Limit

Table 10 shows the acute exposure limits for arsenic as defined by the regulatory agencies.

Table 10 Acute Inhalation Exposure Limits for Arsenic

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	0.1	1-hour	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	0.19	4-hour	OEHHA (2007a)
OMOE	0.3	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The AENV (2007, Website) recommends a 1-hour AAQO for arsenic of 0.1 µg/m^3. This objective was adopted from the Texas Commission on Environmental Quality (TCEQ), which developed its short-term Effects Screening-Level (ESL) based on the ACGIH 8-hour TLV-TWA (Threshold Limit Value – Time Weighted Average) for occupational exposure of 0.01 mg/m^3 (AENV 2004a). The TLV-TWA is based on consistent evidence from numerous epidemiologic studies linking cancer excesses with occupational exposures of smelter workers and pesticide workers and linking skin cancer excesses with persons who used arsenical compounds for medicinal reasons or who drank water contaminated with arsenic (ACGIH 1991). In the derivation of the Texas short-term effects screening-level, the TLV-TWA was divided by an uncertainty factor of 100 (AENV 2004a). Given that the TLV-TWA is based on the chronic end-point of cancer, the AENV AAQO was not used in the acute effects assessment of arsenic.

The OEHHA (1999b, 2007a) provides an acute REL of 0.19 µg/m^3 for arsenic and inorganic arsenic compounds based on reproductive/developmental effects in mice. Pregnant mice were exposed to 0.26, 2.9 or 28.5 mg/m^3 of arsenic trioxide (As_2O_3) via inhalation for four hours per day on gestational days 9, 10, 11 and 12. A LOAEL of 0.26 mg/m^3 As_2O_3 or 0.19 mg/m^3 arsenic was identified based on decreased fetal weight (OEHHA 1999b). The OEHHA (1999b) applied an uncertainty factor of 1,000 to the LOAEL to account for interspecies variability (10-fold), intra-species variability (10-fold) and use of a LOAEL (10-fold). The acute REL of 0.19 µg/m^3 was conservatively used as a 1-hour exposure limit in the acute effects assessment of arsenic.

3.6.2 Chronic Exposure Limit(s)

Table 11 shows the chronic exposure limits for arsenic as defined by the regulatory agencies.

Table 11 Chronic Inhalation Exposure Limits for Arsenic

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	0.0016	RsC	Health Canada (2004b)
RIVM	1.0	RfC	RIVM (2001)
U.S. EPA	0.002	RsC	U.S. EPA (1998b, Website)
WHO	0.0067	RsC	WHO (2000, Website)

— = Not available.

Health Canada (2004b) provides an inhalation unit risk of 6.4 per mg/m^3 for lung cancer. This inhalation unit risk was derived from Tolerable Dose (TD_{05}) for inhaled arsenic of 7.83 µg/m^3 (CEPA 1993a). Three studies that showed arsenic-induced cancer in workers were examined by Health Canada in its assessment:

- Tacoma copper smelter in Washington (Enterline et al. 1987);
- Anaconda smelter in Montana (Higgins et al. 1986); and
- Ronnskar smelter in Sweden (Jarup et al. 1989).

The TD_{05} was derived from the Higgins et al. (1986) study, which provided the most conservative estimate of respiratory cancer potency. A negative exponential growth curve was used to describe the concave-downward relationship between the arsenic concentration in air and mortality from respiratory cancer. Excess risk of respiratory cancer was determined by Health Canada using the predicted curve and age-adjusted mortality rates for the Canadian population associated with lung cancer (CEPA 1993a). The resulting RsC of 0.0016 µg/m^3 represents the daily dose via inhalation that is associated with an increased cancer risk of 1 in 100,000. The RsC is equivalent to an inhaled dose of 0.00036 µg/kg bw/d based on an adult body weight of 70.7 kg and inhalation rate of 15.8 m^3/d (Health Canada 2004a).

Given that arsenic could persist or bioaccumulate in the environment, an oral exposure limit was required (Table 12).

Table 12 Chronic Oral Exposure Limits for Arsenic

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
ATSDR	0.3	RfD	ATSDR (2006a)
Health Canada	0.0060	RsD	Health Canada (2004b)
RIVM	1	RfD	RIVM (2001)
U.S. EPA	0.0067	RsD	U.S. EPA (1998b, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

Health Canada (2006) recommends an oral RsD of 0.006 µg/kg bw/d based on the incidence of internal cancers associated with the ingestion of arsenic in drinking water. A statistical analysis was conducted by Morales et al. (2000) on data collected in a southwestern Taiwan ecological study to estimate the risk of cancer to the bladder, liver and lungs from exposure to arsenic in drinking water. Morales et al. (2000) fit nine Poisson-type models and one Weibull model to the data collected in the ecological study. In its quantitative risk assessment, Health Canada (2006) selected a Poisson model that included an external unexposed comparison population. The Health Canada (2006) model analyzed the data provided by Morales et al. (2000) and derived a range of unit risks with the liver cancer unit risk (3.06×10^{-5}) as its lower bound and the lung cancer unit risk (3.85×10^{-5}) as its upper bound. The 95% upper-bound value is often reported for epidemiological data as it quantifies the variability in the unit risk due to the variability in the study population (i.e., individual differences in metabolism, drinking rates, bodyweight). Health Canada (2006) derived a concentration of 0.3 µg/L arsenic in drinking water based on the 95% upper-bound unit risk. This concentration of arsenic in drinking water is considered representative of an "essentially negligible" level of risk. Health Canada (2006) defines the term "essentially negligible" as a range from one new cancer above background per 100,000 people to one new cancer above background per 1,000,000 people. Assuming an adult water ingestion rate of 1.5 L/d and an adult body weight of 70.7 kg, the concentration of 0.3 µg/L of arsenic in drinking water is equivalent to a dose of 0.006 µg/kg bw/d (Health Canada 2004a). This oral RsD was incorporated in the chronic effects assessment of arsenic.

For incorporation in the multiple exposure pathway model, an inhalation bioavailability of 100% (assumed), oral bioavailability of 41% and dermal bioavailability of 3% were applied (RAIS 2007, Website).

3.7 BARIUM

3.7.1 Acute Exposure Limit

Table 13 shows the acute exposure limits for barium as defined by the regulatory agencies.

Table 13 Acute Inhalation Exposure Limits for Barium

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	—	—	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	—	—	OEHHA (2007a)
OMOE	10	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The OMOE (2005a) provides a 24-hour standard for total water soluble barium; however, no scientific basis was provided. As a result, the study team is unable to comment on the scientific merit of this standard and did not use it in the short-term assessment of barium.

Acute criteria or guidelines have not been established by any of the other regulatory agencies, nor has an intermediate MRLs or short-term occupational limit values (i.e., STEL and Ceiling) (ATSDR 2006a; ACGIH 2006a).

Due to the lack of defensible acute inhalation exposure limits, an acute effects assessment was not completed for barium. As a result, barium was assessed on a chronic basis only.

3.7.2 Chronic Exposure Limit(s)

Table 14 shows chronic exposure limits for barium as defined by the regulatory agencies.

Table 14 Chronic Inhalation Exposure Limits for Barium

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	1.0	RfC	RIVM (2001)
U.S. EPA	—	—	U.S. EPA (1998c, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

The RIVM (2001) recommends Tolerable Concentration in Air (TCA) of 1 µg/m^3 based on cardiovascular effects in a subchronic inhalation rat study. Male rats were exposed to insoluble barium carbonate dust for four hours per day, six days per week for four months (RIVM 2001). A No-Observed-Adverse-Effect Concentration (NOAEC) of 1.15 mg/m^3 of barium carbonate was adjusted to continuous exposure (4 hours/24 hours x 6 days/7 days) to a $NOAEC_{ADJ}$ of 0.16 mg/m^3 of barium carbonate. This is equivalent to a NOAEC of 0.11 mg/m^3 of barium (RIVM 2001). The RIVM (2001) applied an uncertainty factor of 100 to account for interspecies variability (10-fold) and intra-species variability (10-fold). Kinetic studies demonstrate that absorption of insoluble and soluble barium salts do not differ; thus, the RIVM (2001) recommends a TCA of 1 µg/m^3 for both soluble and insoluble barium salts. However, the TCA is based on a subchronic inhalation study and the RIVM did not make an adjustment for the extrapolation of subchronic to chronic exposure. An additional uncertainty factor

of 10 should be applied to account for the use of a subchronic study, which results in a modified TCA of 0.1 µg/m^3.

The U.S. EPA (1998c, Website) reviewed the study used by the RIVM to determine the TCA. The U.S. EPA (1998c, Website) states that their confidence in this study is very low due to poor reporting of the study design and results. As a result, the U.S. EPA (1998c, Website) concluded that a chronic RfC could not be derived based on this study. Based on the U.S. EPA's review of this study, the RIVM TCA was not used in the chronic effects assessment. As such, the toxicity search was expanded to include oral exposure limits (Table 15).

Table 15 Chronic Oral Exposure Limits for Barium

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
ATSDR	600	RfD	ATSDR (2006a)
Health Canada	16	RfD	Health Canada (2004b)
RIVM	20	RfD	RIVM (2001)
U.S. EPA	200	RfD	U.S. EPA (2005b, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

The Health Canada (2004b) oral Tolerable Daily Intake (TDI) of 16 µg/kg bw/d was developed from the Canadian drinking water quality guideline of 1 mg/L. The Maximum Acceptable Concentration (MAC) for barium in water was developed based on a NOAEL of 7.3 mg/L from the most sensitive epidemiological study (Health Canada 1990). Adverse effects on blood pressure and increases in the prevalence of cardiovascular disease were not observed in a population ingesting water containing a mean concentration of 7.3 mg/L (Brenniman and Levy 1985). Health Canada (1990) applied an uncertainty of 10 to the NOAEL to account for intra-species variability, resulting in a MAC of 0.73 mg/L. The MAC of 0.73 mg/L was used to derive the TDI of 16 µg/kg bw/d, assuming an adult water ingestion rate of 1.5 L/d and an adult body weight of 70.7 kg (Health Canada 2004). It is important to note that the TDI is based on a study where no effects were observed.

The RIVM (2001) provides a TDI of 20 µg/kg bw/d based on a NOAEL of 0.2 mg/kg bw/d in drinking water with no clear effect observed in human volunteers. An uncertainty factor of 10 was applied to the NOAEL to derive the TDI (RIVM 2001). Given that the RIVM does not provide the source of the study, the length of exposure or the range of administered doses associated with the TDI and uses a study for which no clear effect level was identified, the RIVM guideline was not used in the long-term effects assessment of barium.

The U.S. EPA (2005b, Website) provides a more recent assessment of the oral toxicity of barium. The derivation of the oral RfD was based on the same Brenniman and Levy (1985) study; however, the U.S. EPA (2005b, Website) recently selected a new principal study and critical effect and used benchmark dose modelling to derive the oral RfD. There is conflicting evidence whether or not barium exposure may induce hypertensive effects and two human studies, including the Brenniman and Levy (1985) study, did not find any effects on hypertension (U.S. EPA 2005b, Website). The U.S. EPA (2005b, Website) concluded that available data indicates that renal toxicity is likely to be the most sensitive endpoint. Thus, the oral RfD of 200 µg/kg bw/d is based on nephropathy observed in a two-year drinking water study in mice (U.S. EPA 2005b, Website).

B6C3F1 mice were administered 0, 500, 1,250 and 2,500 ppm barium chloride dihydrate in drinking water for two years (NTP 1994). The estimated doses were 0, 30, 75 and 160 mg barium/kg/d for male mice and 0, 40, 90 and 200 mg barium/kg/d for female mice (NTP 1994). The U.S. EPA (2005b, Website) calculated a Benchmark Dose (BMD_{05}) corresponding to a 5% extra risk in renal lesions in male mice of 83 mg/kg/d and a lower 95% confidence limit ($BMDL_{05}$) of 63 mg/kg/d. An uncertainty factor of 300 was applied to the $BMDL_{05}$ to account for interspecies variability (10-fold), intra-species variability (10-fold) and deficiencies in the database (3-fold). Database deficiencies include lack of a two-generation reproductive toxicity study or adequate investigation into developmental toxicity and lack of knowledge regarding the potential for barium deposition in bone tissue to produce adverse effects (U.S. EPA 2005b, Website).

Given that the U.S. EPA (2005b, Website) provides a more recent toxicological evaluation of barium which takes into account the same study used by Health Canada, the U.S. EPA RfD of 200 µg/kg bw/d was used in the chronic effects assessment of barium. The ATSDR (2005a) also reviewed barium in 2005 and selected the same study as the U.S. EPA to derive its chronic oral MRL. The ATSDR (2005a) predicted similar $BMDL_{05}$ values, but did not apply the additional uncertainty factor of 3 for database deficiencies. The oral RfD of 200 µg/kg bw/d was used to calculate an inhalation exposure limit of 14 µg/kg bw/d or 63 $\mu g/m^3$ based on the following adjustments and assumptions:

- inhalation bioavailability of 100% (assumed) and oral bioavailability of 7% (RAIS 2007, Website);
- adult body weight of 70.7 kg (Health Canada 2004a); and
- adult inhalation rate of 15.8 m^3/d (Health Canada 2004a).

Given that barium could persist or bioaccumulate in the environment, an oral exposure limit was required. The oral RfD of 200 µg/kg bw/d was used in the oral assessment of barium.

It was conservatively assumed that 100% of inhaled barium is absorbed. Oral bioavailability in humans was assumed to be 7% and dermal bioavailability was assumed to be 0.1% for this assessment (RAIS 2007, Website).

3.8 BENZENE

3.8.1 Acute Exposure Limit

Table 16 shows the acute exposure limit for benzene as defined by the regulatory agencies.

Table 16 Acute Inhalation Exposure Limits for Benzene

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	30	1-hour	AENV (2007, Website)
ATSDR	30	24-hour	ATSDR (2006a)
OEHHA	1,300	6-hour	OEHHA (2007a)
OMOE	—	—	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The AENV (2007, Website) provides a 1-hour AAQO of 30 µg/m^3 for benzene; however, the AAQO was adopted from the TCEQ and the specific basis was not provided. As a result, the study team is unable to comment on the scientific merit of this limit and thus it was not used in the acute effects assessment.

The ATSDR (2005b, 2006a) provides an acute MRL of 0.009 ppm (0.03 mg/m^3) based on immunological effects. Male C57BL/6J mice (7 or 8 per concentration) were exposed to 0, 10.2, 31, 100, or 301 ppm (0, 32.6, 99, 320, or 960 mg/m^3) benzene in whole-body dynamic inhalation chambers for six hours per day on six consecutive days (ATSDR 2005b). The control group was exposed to filtered, conditioned air only. Significant depression of femoral lipopolysaccharide-induced B-colony-forming ability was observed at the 10.2 ppm exposure level in the absence of a significant depression of total number of B cells. Peripheral lymphocyte counts were depressed at all exposure levels.

The ATSDR (2005b) adjusted A LOAEL of 10.2 ppm (32.6 mg/m^3) from intermittent to continuous exposure (6 hours/24 hours) to a concentration of

2.55 ppm (8.16 mg/m^3). The duration-adjusted LOAEL ($LOAEL_{ADJ}$) was converted to a Human Equivalent Concentration ($LOAEL_{HEC}$) for a category 3 gas causing respiratory effects. The average ratio of the animal-blood: air partition coefficient would be greater than 1; thus, a default value of 1 was used in calculating the HEC (ATSDR 2005b). As a result, a $LOAEL_{HEC}$ of 2.55 ppm (8.16 mg/m^3) was also identified. The ATSDR (2005b) applied a cumulative uncertainty factor of 300 to the $LOAEL_{HEC}$ to account for interspecies variability (3-fold), intra-species variability (10-fold) and use of a LOAEL (10-fold). A factor of 3 was applied for the extrapolation of laboratory animal data to humans since the calculation of a HEC addressed the pharmacokinetic aspects of the interspecies uncertainty factor. Accordingly, only the pharmacodynamic aspects of uncertainty remain as a partial factor for interspecies uncertainty. The acute inhalation MRL of 30 µg/m^3 was used as a 24-hour limit in the acute effects assessment of benzene.

3.8.2 Chronic Exposure Limit(s)

Table 17 shows the chronic exposure limits for benzene as defined by the regulatory agencies.

Table 17 Chronic Inhalation Exposure Limits for Benzene

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	9.6	RsC	ATSDR (2006a)
Health Canada	3	RsC	Health Canada (2004b)
RIVM	2	RsC	RIVM (2001)
U.S. EPA	1.3 to 4.5	RsC	U.S. EPA (2000, Website)
WHO	1.7	RsC	WHO (2000, Website)

— = Not available.

An RsC of 3 ug/m^3 is reported by Health Canada (2004b; CEPA 1993b) based on an inhalation unit risk of 0.0033 per mg/m^3. This RsC represents the daily dose via inhalation that is associated with an increased cancer risk of 1 in 100,000.

The WHO (2000, Website) provides an RsC of 1.7 ug/m^3, which is associated with an increased cancer risk of one in 100,000. Using multiplicative risk estimates and a cumulative exposure model, a unit risk for lifetime exposure of 1.4 to 1.5 x 10^{-5} per ppb was derived with the Paustenbach exposure matrix and 2.4 x 10^{-5} per ppb with the Crump and Allen exposure matrix (WHO 2000, Website). These values equate to unit risks that range from 4.4 x 10^{-6} to 7.5 x 10^{-6} per µg/m^3. From this the WHO (2000, Website) selected a representative unit risk of 6 x 10^{-6} per µg/m^3.

The U.S. EPA (2000, Website) presents a range of potential carcinogenic risks from inhalation of benzene. Inhalation unit risks of 2.2 x 10^{-6} to 7.8 x 10^{-6} per µg/m^3 were extrapolated based on a low-dose linear model using maximum likelihood estimates for leukaemia in humans (U.S. EPA 2000, Website). The inhalation unit risks equate to an RsC of 1.3 to 4.5 µg/m^3 associated with a risk level of one in 100,000 (U.S. EPA 2000, Website). The RsC of 1.3 µg/m^3 was selected as the chronic inhalation limit for benzene as it is the most conservative of the values presented within this range.

Benzene was not incorporated into the multiple pathway exposure assessment since it did not exceed the persistence and bioaccumulation parameters established by Environment Canada (2008, Website). As a result, a chronic oral exposure limit was not required for benzene.

3.9 BERYLLIUM

3.9.1 Acute Exposure Limit

Table 18 shows the acute exposure limit for beryllium as defined by the regulatory agencies.

Table 18 Acute Inhalation Exposure Limits for Beryllium

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	—	—	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	—	—	OEHHA (2007a)
OMOE	0.01	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The OMOE (2005a) provides a 24-hour standard of 0.01 µg/m^3 for beryllium and compounds protective of health. The scientific basis of these limits is not provided. As a result, the study team is unable to comment on the scientific merit of these standards and did not use them in the short-term inhalation assessment of beryllium.

An acute criterion or guideline has not been established by any of the other regulatory agencies for beryllium, thus the toxicity search was expanded to include intermediate MRLs or short-term occupational limit values (i.e., STEL and Ceiling) (ATSDR 2006a; ACGIH 2006a).

The ACGIH (1997, 2006a) recommends a STEL of 0.01 mg/m^3 protective of acute beryllium disease. Reported cases of acute beryllium disease were found to be associated with exposures above 100 $\mu g/m^3$ and a group of eight workers exposed below 15 $\mu g/m^3$ did not develop acute beryllium disease (ACGIH 1997). Based on the given information, the ACGIH (1997) concluded a TLV-STEL of 10 $\mu g/m^3$ is appropriate. The STEL equates to a 15-minute air concentration that should not be exceeded at any time during a workday (ACGIH 2006a). The 15-minute STEL can be adjusted to an equivalent 1-hour concentration using a modified Haber's Law (OEHHA 1999a).

$$C_{ADJ}^{n} \times T_{ADJ} = C^{n} \times T$$

$$C^{1} \times 60 \text{ minutes} = (10\ \mu g/m^3)^{1} \times 15 \text{ minutes}$$

Where:

C_{ADJ} = duration-adjusted concentration

T_{ADJ} = desired time of exposure (60 minutes)

C = concentration of exposure (10 $\mu g/m^3$)

T = time of exposure (15 minutes)

n = chemical-specific modification factor designed to account for the toxicity of a chemical being concentration and/or duration dependent. The OEHHA (1999a) recommends using a default *n* value of 1 in the adjustment for less than 1-hour exposure.

Based on the above conversion factor, the STEL was adjusted to a concentration of 2.5 $\mu g/m^3$. A cumulative uncertainty factor of 10 was applied to the duration-adjusted STEL to account for intra-species variability (10-fold). On this basis, the adjusted STEL of 0.25 $\mu g/m^3$ was adopted as a 1-hour exposure limit in the acute effects assessment.

The ACGIH (2006a,b) reports a Notice of Intended Changes for beryllium and compounds. A TLV-STEL of 0.0002 mg/m^3 is recommended for beryllium as inhalable particulate matter. In an occupational study, the percentage of samples with excursions greater than 0.2 $\mu g/m^3$ was greater for job categories that exhibited significant increases in beryllium sensitization and chronic beryllium disease (ACGIH 2006b). A proposed STEL of 0.2 $\mu g/m^3$ was established to minimize the excursions above this value. Given that this value is provisional and its use is not supported by the ACGIH at this time, the proposed STEL was not used in the acute effects assessment of beryllium.

3.9.2 Chronic Exposure Limit(s)

Table 19 shows the chronic exposure limits for beryllium as defined by the regulatory agencies.

Table 19 Chronic Inhalation Exposure Limits for Beryllium

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	—	—	RIVM (2001)
U.S. EPA	0.02 0.004	RfC RsC	U.S. EPA (1998d, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

The U.S. EPA (1998d, Website) provides an inhalation RsC of 0.004 µg/m^3 based on lung cancer in male workers following occupational exposure. Estimated lower and upper bounds of exposure (100 and 1,000 µg/m^3) to beryllium oxide from an epidemiology study were used to estimate the lifetime cancer risk. The exposure concentrations were adjusted for duration of daily (8 hours/24 hours) and annual (240 days/365 days) exposure and by a ratio of years of exposure (f) to years at risk (L) (i.e., from onset of employment to termination or follow-up; U.S. EPA 1998d, Website). The inhalation unit risk of 2.4 x 10^{-3} per µg/m^3 equates to an RsC associated with a risk level of one in 100,000 (U.S. EPA 1998d, Website). The RsC of 0.004 µg/m^3 was used in the chronic effects assessment of beryllium. The RsC is equivalent to an inhaled dose of 0.00089 µg/kg bw/d based on an adult body weight of 70.7 kg and inhalation rate of 15.8 m^3/d (Health Canada 2004a).

Given that beryllium could persist or bioaccumulate in the environment, an oral exposure limit was required (Table 20).

Table 20 Chronic Oral Exposure Limits for Beryllium

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
ATSDR	2	RfD	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	—	—	RIVM (2001)
U.S. EPA	2	RfD	U.S. EPA (1998d, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

The U.S. EPA (1998d, Website) and the ATSDR (2002, 2006a) recommend RfDs of 2 µg/kg bw/d based on the same principal study. Beagle dogs were administered 0, 5, 50 or 500 ppm beryllium as beryllium sulphate tetrahydrate in their diet of 172 weeks (Morgareidge et al. 1976). Due to overt signs of toxicity, the 500 ppm group was terminated after 33 weeks and a group fed 1 ppm beryllium in the diet for 143 weeks was included. The administered concentrations are equivalent to doses of 0, 0.02, 0.1, 1 and 12 mg/kg/d for male dogs and 0, 0.03, 0.2, 1 and 17 mg/kg/d for female dogs (ATSDR 2002; U.S. EPA 1998d, Website). A benchmark dose approach was used by the ATSDR (2002) to identify a BMDL of 0.56 mg/kg-day from the dose-response data for inflammatory lesions in the gastrointestinal tract. A cumulative uncertainty factor of 300 was applied to account for interspecies variability (10-fold) and intra-species variability (10-fold) and uncertainty in the toxicological database relating to whether or not the BMDL represents a NOAEL (3-fold).

Similarly, the U.S. EPA (1998d, Website) used dose-response modelling to derive a BMD_{10} corresponding to a 10% increase in small intestine lesions of 0.46 mg/kg/d. The U.S. EPA (1998d, Website) applied an uncertainty factor of 300 to the BMD_{10} to account for interspecies variability (10-fold), intra-species variability (10-fold) and database deficiencies (3-fold). The partial uncertainty factor was included for database deficiencies because human oral toxicity data is not available and reproductive/developmental and immunotoxicologic endpoints have not been adequately assessed in animals (U.S. EPA 1998d, Website). The U.S. EPA and ATSDR RfD of 2 µg/kg bw/d was used in the oral assessment of beryllium.

It was conservatively assumed that 100% of inhaled beryllium is absorbed. Oral bioavailability in humans was assumed to be 1% and dermal bioavailability was assumed to be 0.1% for this assessment (RAIS 2007, Website).

3.10 CADMIUM

3.10.1 Acute Exposure Limit

Table 21 shows the acute exposure limits for cadmium as defined by the regulatory agencies.

Table 21 Acute Inhalation Exposure Limits for Cadmium

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	—	—	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	—	—	OEHHA (2007a)
OMOE	2	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The OMOE (2006a, 2005a) provides a 24-hour standard for cadmium protective of health based on 1/100th of the TLV. No further scientific basis is provided for this standard. However, the OMOE (2006a) has recently proposed a 24-hour standard of 0.025 µg/m^3 for cadmium based on kidney effects. The OMOE (2006a) derived this 24-hour standard from the annual guideline of 5 ng/m^3 developed by the European Commission (EC). The EC considered the non-carcinogenic effects on the kidney to be the critical indicator of inhalation exposure (OMOE 2006a). A range of 100 to 499 µg/m^3-years of cumulative exposure was calculated as the level at which adverse kidney effects could be observed in most workers (Thun et al. 1991). The lower end of the range was selected as a LOAEL of 100 µg/m^3. The EC adjusted the LOAEL to continuous exposure (8 hours/24 hours x 225 days/365 days x 1 year/75 years) to a $LOAEL_{ADJ}$ of 270 ng/m^3 (OMOE 2006b). An uncertainty factor of 50 was applied to the duration-adjusted LOAEL of 270 ng/m^3 to account for use of a LOAEL (5-fold) and intra-species variability (10-fold).

The EC standard was developed based on the Thun et al. (1991) study which provides pooled data from seven epidemiological studies examining cumulative or multi-year cadmium exposure (OMOE 2006a). Using chronic data to derive an acute exposure limit is considered overly conservative and inappropriate. As a result, the 24-hour standard provided by the OMOE (2006a) was not used in the acute effects assessment of cadmium.

An acute criterion or guideline has not been established by any of the other regulatory agencies for cadmium, nor has an intermediate MRL or short-term occupational limit value (i.e., STEL and Ceiling) (ATSDR 2006a; ACGIH 2006a). As such, cadmium was evaluated under the chronic effects assessment only.

3.10.2 Chronic Exposure Limit(s)

Table 22 shows the chronic exposure limits for cadmium as defined by the regulatory agencies.

Table 22 Chronic Inhalation Exposure Limits for Cadmium

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	0.001	RsC	Health Canada (2004b)
RIVM	—	—	RIVM (2001)
U.S. EPA	0.006	RsC	U.S. EPA (1992, Website)
WHO	0.005	RfC	WHO (2000, Website)

— = Not available.

An RsC of 0.001 µg/m^3 was developed by Health Canada (2004b) from a Tumourigenic Concentration (TC_{05}) of 5.1 µg/m^3, which was associated with a 5% increase in lung tumours in rats (CEPA 1994a; Takenaka et al. 1983; Oldiges et al. 1984). A TC_{05} of 2.9 µg/m^3 was calculated by fitting the multi-stage model to the lung tumour incidences observed in the rat (CEPA 1994a). This value was amortized to be constant over the lifetime of the rat, adjusted for the longer than standard lifetime duration of the experiment and a human equivalent concentration calculated, resulting in a TC_{05} of 5.1 µg/m^3 (CEPA 1994a). This objective represents the daily dose via inhalation that is associated with a cancer risk of 1 in 100,000.

The WHO (2000, Website) provides a guideline value of 0.005 µg/m^3 based on the finding that the cadmium body burden of the general population in some parts of Europe cannot be further increased without endangering renal function. As a result, the WHO (2000, Website) recommends a guideline of 0.005 µg/m^3 that will prevent any further increase of cadmium in agricultural soils that are likely to increase the dietary intake of future generations. As this guideline is not specifically health-based, it was not used in the health risk assessment.

The U.S. EPA (1992, Website) has developed an RsC of 0.006 µg/m^3 from an inhalation unit risk of 0.0018 per µg/m^3. The inhalation unit risk is based on lung, trachea and bronchitis cancer deaths in occupationally exposed workers (Thun et al. 1985). Effects of arsenic and smoking were accounted for in the quantitative analysis for cadmium effects. This objective represents the daily dose via inhalation that is associated with an increased cancer risk of 1 in 100,000.

The U.S. EPA also calculated an inhalation unit risk for cadmium based on the Takenaka et al. (1983) study, which was one of the key studies in the Health Canada assessment. The U.S. EPA (1992, Website) calculated an RsC of 0.092 per µg/m^3, which is more conservative. However, the U.S. EPA (1992, Website) concluded that use of available human data was more reliable due to species variations in response and the type of exposure (cadmium salt vs. cadmium fume and cadmium oxide). The RsC of 0.006 µg/m^3 was selected in

the chronic effects assessment of cadmium as it is based upon human data, which has been noted to be more reliable with respect to cadmium. This RsC is equivalent to an inhaled dose of 0.0013 µg/kg bw/d based on an adult body weight of 70.7 kg and adult inhalation rate of 15.8 m^3/d (Health Canada 2004a).

Given that cadmium could persist or bioaccumulate in the environment, an oral exposure limit was required (Table 23).

Table 23 Chronic Oral Exposure Limits for Cadmium

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
ATSDR	0.2	RfD	ATSDR (2006a)
Health Canada	0.8	RfD	Health Canada (2004b)
RIVM	0.5	RfD	RIVM (2001)
U.S. EPA	0.5 (water) 1.0 (food)	RfD	U.S. EPA (1994a, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

The ATSDR (1999a, 2006a) provides a chronic MRL of 0.2 µg/kg bw/d for renal damage (proteinuria) in residents of the Katchashi River basin in the Ishikawa Prefecture in Japan. Residents were exposed to cadmium through ingestion of locally produced rice for one to more than 70 years (Nogawa et al. 1989). The ATSDR (1999a) identified a NOAEL of 0.0021 mg/kg bw/d based on abnormal urinary β2-microglobin concentrations (i.e., more than or equal to 1,000 µg/L or 1,000 µg/g creatinine in morning urine). An uncertainty factor of 10 was applied to the NOAEL to account for intra-species variability (ATSDR 1999a).

Health Canada (2004b) provides a Tolerable Daily Intake (TDI) of 0.8 µg/kg bw/d for cadmium. The TDI was derived by Health Canada based on health considerations; however, the specific basis of its derivation remains unknown. As a result, the study team is unable to comment on the scientific merit of this limit and did not use it in the long-term assessment of cadmium.

The RIVM (2001) provides an oral RfD of 0.5 µg/kg bw/d based on the critical effect of renal tubular dysfunction. The RIVM derives this RfD based on studies that indicate the lowest level of cadmium in kidney cortex at which renal effects can be detected in approximately 4% of the population is 50 mg/kg. This corresponds to a daily intake of 1 µg/kg bw/d, assuming 40 to 50 years of intake of 50 µg of cadmium per day (RIVM 2001). The RIVM (2001) applied an uncertainty factor of 2, resulting in an oral RfD of 0.5 µg/kg bw/d.

The U.S. EPA (1994a, Website) has developed an RfD for food consumption of 1 µg/kg bw/d for significant proteinuria in human studies involving chronic exposures. A concentration of 200 µg cadmium per gram wet human renal cortex was identified as the highest renal level not associated with significant proteinuria. A NOAEL of 0.01 mg/kg bw/d was calculated, assuming that 0.01% of the cadmium burden is eliminated per day and 2.5% of cadmium in food is absorbed (U.S. EPA 1994a, Website). The U.S. EPA (1994a, Website) applied an uncertainty factor of 10 to the NOAEL to account for intra-species variability.

The no effect concentration was based on data obtained from many studies on the toxicity of cadmium in both human and animals and not any one study in particular. These data also allowed for the calculation of pharmacokinetic parameters of cadmium absorption, distribution, metabolism and elimination. All of this information resulted in a high degree of confidence in the database and a high degree of confidence in the RfD (U.S. EPA 1994a, Website). Because the U.S. EPA RfD for food consumption takes into account multiple animal and human studies and has a high degree of confidence associated with it, this RfD of 1 µg/kg bw/d was used in the long-term assessment of cadmium.

For incorporation in the multiple exposure pathway model, an inhalation bioavailability of 100% (assumed), oral bioavailability of 1% (RAIS 2007, Website) and dermal bioavailability of 0.1% (RAIS 2007, Website) were assumed.

3.11 CARBON DISULPHIDE GROUP

3.11.1 Acute Exposure Limit

Table 24 shows the acute exposure limits for the carbon disulphide group as defined by the regulatory agencies.

Table 24 Acute Inhalation Exposure Limits for the Carbon Disulphide Group

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	30	1-hour	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	6,200	6-hour	OEHHA (2007a)
OMOE	330	24-hour	OMOE (2005a)
WHO	100	24-hour	WHO (2000, Website)

— = Not available.

Both the AENV (2007, Website) 1-hour AAQO and the OMOE (2005a) 24-hour AAQC for carbon disulphide are based on odour and thus were not employed in the short-term assessment of the carbon disulphide group.

The WHO (2000, Website) has developed a 24-hour guideline for carbon disulphide of 100 µg/m^3 based on the lowest concentration at which adverse effects were observed in occupational exposure. However, the lowest observed concentration of 10 mg/m^3 is based on a 10- to 15-year duration of exposure and therefore is not appropriate for the derivation of an acute exposure limit. Thus, this guideline was not used in the short-term assessment of the carbon disulphide group.

The OEHHA (1999c, 2007a) acute REL of 6,200 µg/m^3 for carbon disulphide is based on reproductive, developmental and Central Nervous System (CNS) effects in rats. Pregnant rats were exposed via inhalation to concentrations of 0, 100, 200, 400 and 800 ppm for six hours per day on days six to 20 of gestation (OEHHA 1999c). Significant reductions in fetal weight were reported at 400 ppm and the NOAEL was identified as 200 ppm (620 mg/m^3). The OEHHA (1999c) applied a cumulative safety factor of 100 to the NOAEL to account for interspecies variability (10-fold) and intra-species variability (10-fold). The 6-hour REL of 6,200 µg/m^3 was conservatively used in the acute effects assessment as a 1-hour exposure limit.

3.11.2 Chronic Exposure Limit(s)

Table 25 shows the chronic exposure limits for the carbon disulphide group as defined by the regulatory agencies.

Table 25 Chronic Inhalation Exposure Limits for the Carbon Disulphide Group

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	930	RfC	ATSDR (2006a)
Health Canada	100	RfC	Health Canada (2004c)
RIVM	—	—	RIVM (2001)
U.S. EPA	700	RfC	U.S. EPA (1995a, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

Health Canada (2004c) provides a chronic inhalation exposure limit of 100 µg/m^3 based on the Tolerable Concentration (TC_{05}) for inhalation exposure recommended for carbon disulphide (CEPA 2000a). This TC_{05} was derived from the lower benchmark concentration of 20 mg/m^3, associated with a 5% adverse

response for peroneal motor nerve conduction velocity in occupationally exposed workers (Johnson et al. 1983; CEPA 2000a). The TC_{05} was adjusted by Health Canada for intermittent exposure of eight hours per workday and five days per workweek (8 hours/24 hours x 5 days/7 days). A safety factor of 50 was also applied by Health Canada in the derivation of the human exposure limit to account for intra-species variability (10-fold) and for potential effects on neurobehavioral development (5-fold). The resultant TC_{05} of 100 $\mu g/m^3$ was used as the chronic inhalation exposure limit for the carbon disulphide group.

The carbon disulphide group was not assessed through multiple pathways since its physical and chemical parameters did not exceed any of the persistence and bioaccumulation parameters established by Environment Canada (2008, Website). On this basis, a chronic oral exposure limit was not required for carbon disulphide.

3.12 CARBON MONOXIDE

Chemicals of potential concern that are governed and defined at the federal government level in the form of either National Ambient Air Quality Objectives (NAAQOs) or as a Canada-Wide Standard (CWS) were not subjected to the typical screening process. Instead, the AAQOs adopted by the AENV (2007, Website) from Health Canada were given priority. Carbon monoxide is one of these chemicals.

3.12.1 Acute Exposure Limit

The AENV (2007, Website) provides a 1-hour AAQO of 15,000 $\mu g/m^3$ and an 8-hour AAQO of 6,000 $\mu g/m^3$ for carbon monoxide. These AAQOs were adopted from the Canadian Environmental Protection Act and Federal Provincial Advisory Committee (CEPA/FPAC) Working Group on Air Quality Objectives and Guidelines, who recommends maximum desirable, acceptable and tolerable objectives for carbon monoxide. The Alberta objectives are based on the maximum desirable levels (i.e., the lowest objective). These objectives were developed to protect the subpopulation sensitive to cardio-respiratory effects (CEPA/FPAC 1994).

As there are no 24-hour guidelines available, the acute assessment was completed on a 1-hour and 8-hour basis only.

3.12.2 Chronic Exposure Limit(s)

No regulatory exposure limits were available for chronic exposure to carbon monoxide. The critical effect of carbon monoxide (CO) exposure is the formation of carboxyhemoglobin (COHb) in blood. As COHb concentrations reach a steady-state after six to eight hours of exposure, carbon monoxide exposure for longer periods of time (i.e., chronic exposure) is not expected to cause accumulation of COHb in the blood (WHO 2000, Website).

Epidemiological studies have identified associations between ambient low-level carbon monoxide concentrations and various health effects (Burnett et al. 2000; Moolgavkar 2000). However, the results across studies are inconsistent and it has been suggested that carbon monoxide might represent only a surrogate compound for particulate emissions from mobile sources (Sarnat et al. 2001; Schwartz 1999).

Carbon monoxide was assessed only for the inhalation route of exposure as the principal health effects are strictly related to inhalation.

3.13 CARCINOGENIC POLYCYCLIC AROMATIC HYDROCARBON GROUPS

3.13.1 Acute Exposure Limit

Table 26 shows the acute inhalation exposure limits for the carcinogenic polycyclic aromatic hydrocarbon group as defined by the regulatory agencies.

Table 26 Acute Inhalation Exposure Limits for the Carcinogenic Polycyclic Aromatic Hydrocarbon Groups

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	—	—	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	—	—	OEHHA (2007a)
OMOE	0.0011[(a)]	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

[(a)] Exposure limit is based on benzo(a)pyrene.

— = Not available.

The only individual constituent of the carcinogenic PAHs with a public acute exposure limit is benzo(a)pyrene. The OMOE (2005a) provides a 24-hour standard of 0.0011 µg/m^3 based on the carcinogenic potential for benzo(a)pyrene.

The limit was derived from an annual exposure limit of 0.00022 µg/m^3 for protection against carcinogenic effects using a simple extrapolation factor generally considered to be overly conservative. This limit was not used in the acute effects assessment for the carcinogenic PAH groups as it did not account for the influence of exposure duration on the carcinogenic action of a chemical.

After reviewing available information and determining that there are no available criteria, guidelines or objectives for the carcinogenic PAHs with adequate supporting documentation, the carcinogenic PAHs were not assessed on an acute basis.

3.13.2 Chronic Exposure Limit(s)

Chronic exposure limits are not available for each of the carcinogenic PAH groups as a whole. Thus, the carcinogenic PAH groups were evaluated based on their cancer potency relative to a compound for which toxicity data is available (i.e., benzo(a)pyrene) (Table 27).

Table 27 Chronic Inhalation Exposure Limits for Benzo(a)pyrene

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	0.32	RsC	Health Canada (2004b)
RIVM	—	—	RIVM (2001)
U.S. EPA	—	—	U.S. EPA (1994b, Website)
WHO	0.00012	RsC	WHO (2000, Website)

— = Not available.

The WHO (2000, Website) recommends an inhalation unit risk of 0.087 per µg/m^3 based on epidemiological data from studies in coke-oven workers. The WHO (2000, Website) identified an upper-bound individual lifetime unit risk estimate associated with continuous exposure to 1 µg/m^3 of benzene-soluble compounds of coke-oven emissions in ambient air of 0.00062 per µg/m^3 based on a linearized multi-stage model. Benzo(a)pyrene was selected as an indicator of general PAH mixtures from emissions of coke ovens and similar combustion processes in urban air. In the benzene-soluble fraction of coke oven emissions, 0.71% is reported to be benzo(a)pyrene. On this basis, the lifetime risk of respiratory cancer of 0.087 per µg/m^3 was calculated (WHO 2000, Website), which equates to an RsC of 0.00012 µg/m^3 that is associated with an acceptable incremental lifetime cancer risk of one in 100,000. The WHO RsC was not used in the chronic effects assessment as it is not based on benzo(a)pyrene alone, rather a PAH mixture.

Health Canada (2004b) provides an inhalation unit risk of 0.0033 per µg/m^3, which equates to an RsC of 0.32 µg/m^3. This RsC is associated with an acceptable incremental lifetime cancer risk of development of lung tumours of one in 100,000. The RsC was developed via multi-stage modelling of respiratory tract tumours in Syrian golden hamsters (Thyssen et al. 1981; CEPA 1994b). In the key study, groups of 24 male Syrian golden hamsters were exposed by inhalation (nose only) to 0, 2.2, 9.5, or 45.6 mg/m^3 benzo(a)pyrene for 4.5 hours per day, seven days per week for the first 10 weeks and for three hours per day for the rest of the exposure period (up to 96 weeks).

A decrease in body weight gain in exposed animals was observed during the first 10 weeks of the study; however, from the tenth to the sixtieth week, the body weights of all surviving exposed animals were similar to those of the controls (with the exception of the high exposure group). Mean survival was also decreased in the highest exposure group. The incidences of unspecified tumours of the respiratory tract (nasal cavity, larynx and trachea) were: 0/27 for controls; 0/27 for the low-dose group; 9/26 (35%) for the mid-dose group; and 13/25 (52%) for the high-dose group (Thyssen et al. 1981). Exposure-related neoplasms (unspecified) were present in the pharynx (0, 0, 23 and 56% for control, low-, mid- and high-dose, respectively), esophagus (0, 0, 0 and 8% for control, low-, mid- and high-dose, respectively) and forestomach (0, 0, 4 and 4% for control, low-, mid- and high-dose, respectively). Lung tumours were not observed (Thyssen et al. 1981). The Health Canada RsC of 0.32 µg/m^3 was selected for the chronic inhalation assessment of the carcinogenic PAH group and is equivalent to an inhaled dose of 0.072 µg/kg bw/d (based on the above adjustments).

The carcinogenic PAH groups were identified as a potentially persistent and bioaccumulative chemical in the environmental media. Therefore, they were assessed via multiple exposure pathways and required oral exposure limits (Table 28).

Table 28 Chronic Oral Exposure Limits for Benzo(a)pyrene

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	0.0043	RsD	Health Canada (2004b)
RIVM	0.5	RsD	RIVM (2001)
U.S. EPA	0.0014	RsD	U.S. EPA (1994b, Website)
WHO	0.023	RsD	WHO (2000, Website)

— = Not available.

The U.S. EPA (1994b, Website) provides an oral slope factor of 7.3 per mg/kg bw/d based on the geometric mean of four slope factors obtained by different modelling procedures and multiple data sets from two different studies, including the Neal and Rigdon (1967) study that was used in the Health Canada (1988) assessment. The U.S. EPA (1994b, Website) considered each of these data sets to be acceptable for the derivation of an oral slope factor, but less-than-optimal. As a result, the use of a geometric mean of the four slope factors was preferred because it made use of more of the available data. The four slope factors were calculated as follows:

- The Neal and Rigdon (1967) data was fit to a two-stage dose response model that included a term to permit the modelling of benzo(a)pyrene as its own promoter (modification of Moolgavkar-Venson-Knudson, generalized forms of two-stage model). In this model, the transition rates and the growth rate of preneoplastic cells were both considered to be exposure-dependent. In addition to the Neal and Rigdon (1967) control group, historical control stomach tumour data from a related, but not identical, mouse strain (SWR/J Swill) was used in the modelling (Rabstein et al. 1973). In the historical control data, the forestomach tumour incidence rate was 2/268 and 1/402 for males and females, respectively. The lifetime unit risk for humans was calculated based on the following standard assumptions: mouse food consumption was 13% of its body weight per day, human body weight was assumed to be 70 kg and the assumed body weight of the mouse was 0.034 kg (U.S. EPA 1994b, Website). The standard assumption of surface area equivalence between mice and humans was the cube root of 70 kg/0.034 kg. A conditional upper-bound estimate was calculated to be 5.9 per mg/kg bw/d (U.S. EPA 1994b, Website).
- The same data set as above was used to generate an upper-bound estimate extrapolated linearly from the 10% response point to the background of an empirically fitted dose-response curve (modification of Moolgavkar-Venson-Knudson, generalized forms of two-stage model). An upper-bound was calculated to be 9.0 per mg/kg bw/d (U.S. EPA 1994b, Website).
- To reflect the partial lifetime exposure pattern over different parts of the animals' lifetimes, a generalized Weibull-type dose-response model was selected to assess the Neal and Rigdon (1967) data alone (i.e., excluding the two additional control groups from Rabstein et al.). An upper-bound was calculated to be 4.5 per mg/kg bw/d (U.S. EPA 1994b, Website).
- A linearized multi-stage procedure was used to calculate an upper bound estimate for humans from the Brune et al. (1981) rat data set. Thirty-two Sprague-Dawley (rats/sex/group) were fed 0.15 mg/kg benzo(a)pyrene (reported to be "highly pure") in the diet of either every 9th day or five times per week. These treatments resulted in annual average doses of 6 or 39 mg/kg, respectively. The control group

contained 32 rats per sex. Treatment continued until the rats were moribund or dead; survival was similar in all groups. The combined incidence of tumours of the forestomach, esophagus and larynx was 3/64, 3/64 and 10/64 in the control group, the group fed benzo(a)pyrene every 9th day and the group fed benzo(a)pyrene five times per week, respectively. A trend analysis showed a statistically significant tendency for the proportion of animals with tumours of the forestomach, esophagus or larynx to increase steadily with dose. An oral slope factor of 11.7 per mg/kg bw/d was calculated (U.S. EPA 1994b, Website).

Because the U.S. EPA considered in its development of an oral slope factor (i) different modelling procedures, (ii) multiple data sets from two different studies and (iii) both sexes of more than one strain of mice and species of out bred rodents, the U.S. EPA RsD of 0.0014 µg/kg bw/d was selected as the chronic oral limit for the carcinogenic PAH groups.

The carcinogenic PAH groups were assessed using the Individual PAH Method (IPM), in which health risks are based on the sum of the attributable risks for each individual PAH. The first step in the IPM requires an estimate of the inhalation potency of benzo(a)pyrene and of other PAHs relative to benzo(a)pyrene. This step involves the use of Toxic Equivalency Factors (TEFs) to denote the cancer potency of specific PAH compounds relative to the potency of benzo(a)pyrene (Bostrom et al. 2002). Toxic Equivalency Factors allow large groups of compounds with a common mechanism of action such as PAHs to be assessed when there are limited data available for all but one of the compounds (i.e., benzo(a)pyrene). The TEF-adjusted exposure limits for each of the carcinogenic PAH groups are provided in Table 29 along with the TEF values used.

Table 29 Chronic Exposure Limits for the Carcinogenic Polycyclic Aromatic Hydrocarbon Group

Group	Toxic Equivalency Factor	Modified Inhalation Exposure Limit [µg/m^3]	Modified Oral Exposure Limit [µg/kg bw/d]
Carcinogenic PAH Group 1	1	0.32	0.0014
Carcinogenic PAH Group 2	0.1	3.2	0.014
Carcinogenic PAH Group 3	0.03	10.7	0.047

For incorporation in the multiple exposure pathway model, inhalation bioavailability was assumed to be 100% as no data were identified in the literature regarding the amount of benzo(a)pyrene absorbed via inhalation. The oral bioavailability was assumed to be 31% and dermal bioavailability was assumed to be 13% (RAIS 2007, Website).

3.14 CHROMIUM

3.14.1 Acute Exposure Limit

Table 30 shows acute inhalation exposure limits for chromium as defined by the regulatory agencies.

Table 30 Acute Inhalation Exposure Limits for Chromium

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	1	1-hour	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	—	—	OEHHA (2007a)
OMOE	1.5	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The AENV (2007, Website) provides a 1-hour AAQO of 1 µg/m^3, which was adopted from the Texas Natural Resource Conservation Commission. However, no specific basis of derivation was provided for this limit. Thus, the study team is unable to comment on the scientific merit of this limit and it was not included in the current assessment.

The OMOE (2004, 2005a) provides a 24-hour standard for di-, tri- and hexavalent forms of chromium based on the potential for adverse health effects. However, the OMOE (2004) states that the current standard is inadequate for protection of human health given the potential carcinogenicity of hexavalent chromium. The OMOE (2004) proposes to redefine the scope and level of the existing standard for total chromium to include only trivalent and divalent forms. As such, the OMOE's 24-hour standard was not used in the acute effects assessment.

The toxicity search was therefore expanded to include intermediate MRLs and occupational short-term exposure limits (i.e., STEL, Ceiling) (ATSDR 2006a; ACGIH 2006a).

The ATSDR (2000a, 2006a) has developed an intermediate inhalation MRL of 0.000005 mg/m^3 based on respiratory effects from inhalation exposure to chromic acid (chromium trioxide mist) and other dissolved hexavalent chromium aerosols and mists. Male and female chrome plating workers were exposed to chromic acid for 0.1 to 36 years. Chromium exposures were measured using personal air samplers and stationary equipment positioned close to the chromic

acid baths. Three exposure categories were established: high (average daily concentrations more than 0.002 mg/m^3), low (average daily concentrations less than 0.002 mg/m^3) and mixed (average daily concentrations less than 0.002 mg/m^3 and there were exposures to other acids and metallic salts). A LOAEL of 0.002 mg/m^3 as chromic acid for respiratory effects with a median exposure period of 2.5 years was identified. The ATSDR (2000a) adjusted the LOAEL for continuous exposure (8 hours/24 hours x 5 days/7 days) and applied an uncertainty factor of 100 to account for the use of a LOAEL (10-fold) and for intra-species variability (10-fold). However, the median length of exposure of 2.5 years suggests that the study is largely based on a chronic exposure duration, which is not appropriate for deriving an acute exposure limit. Thus, the intermediate MRL was not used in the acute effects assessment.

There are no other acute exposure limits for total chromium for which supporting documentation is available from any regulatory agencies. As discussed above, the limits that are available are vague, or involved studies that did not distinguish between exposures to chromium (III), chromium (VI) or total chromium. As such, chromium (total) was not assessed on an acute basis.

3.14.2 Chronic Exposure Limit(s)

Table 31 shows the chronic inhalation exposure limits for chromium as defined by the regulatory agencies.

Table 31 Chronic Inhalation Exposure Limits for Chromium

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	0.0009	RsC	Health Canada (2004b)
RIVM	60	RfC	RIVM (2001)
U.S. EPA	—	—	U.S. EPA (1998e, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

Health Canada (2004b) provides an inhalation unit risk of 10.9 per mg/m^3 for chromium (total), which was derived from a TC_{05} of 4.6 µg/m^3 based on mortality due to lung cancer in a cohort of 332 men employed at a chromate production plant between 1931 and 1937 (CEPA 1994c). Workers were exposed to total chromium, soluble (principally hexavalent) or insoluble (principally trivalent) chromium. The TC_{05} is associated with a 5% increase in lung cancer among plant workers. Given that hexavalent chromium was assessed separately and according to the International Association for Research on Cancer (IARC 1997) trivalent chromium is not classifiable as to its carcinogenicity to

humans, Health Canada's unit risk factor was not used to calculate the chronic inhalation exposure limit for chromium (total).

The RIVM (2001) provides a tolerable concentration in air of 60 µg/m^3 based on a NOAEC of 0.6 mg/m^3 for human inhalation exposure to metallic chromium. An uncertainty factor of 10 was applied to the NOAEC to account for intra-species variability. This RfC is equivalent to an inhaled dose of 13 µg/kg bw/d assuming the average adult weighs 70.7 kg and breaths 15.8 m^3/d (Health Canada 2004a). The RIVM inhalation limit of 60 µg/m^3 was used in the chronic effects assessment of chromium (total).

Given that chromium could persist or bioaccumulate in the environment, an oral exposure limit was required (Table 32).

Table 32 Chronic Oral Exposure Limits for Chromium

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	1	RfD	Health Canada (2004b)
RIVM	5	RfD	RIVM (2001)
U.S. EPA	1,500	RfD	U.S. EPA (1998e, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

Health Canada (2004b) provides a TDI of 1 µg/kg bw/d for chromium (total). However, no scientific rationale is provided for the derivation of this guideline. As the study team is unable to comment on the scientific merit of this oral exposure limit, it was not used in the current long-term assessment of chromium (total).

The RIVM (2001) provides a TDI of 5 µg/kg bw/d for soluble chromium (trivalent) compounds. The TDI was derived from a NOAEL of 2.5 mg/kg bw/d in a rat study. An uncertainty factor of 100 was applied to the NOAEL to account for interspecies variability (10-fold) and intra-species variability (10-fold). An additional factor of 5 was applied to account for the time of exposure. Another study conducted in rats identified a chronic NOAEL of 0.46 mg/kg bw/d. An uncertainty factor of 100 was applied to the NOAEL to account for interspecies variability (10-fold) and intra-species variability (10-fold), resulting in a TDI of 4.6 µg/kg bw/d (RIVM 2001). Based on these two studies, the RIVM (2001) elected to maintain a chronic oral exposure limit of 5 µg/kg bw/d for soluble chromium (trivalent) compounds. The RIVM (2001) states that according to the chronic NOAELs, the toxicity of insoluble chromium (trivalent) compounds is approximately 1,000 times less than soluble compounds.

Thus, the RIVM (2001) recommends a TDI of 5,000 µg/kg bw/d for insoluble chromium (trivalent) compounds.

The U.S. EPA (1998e, Website) has developed an RfD of 1,500 µg/kg bw/d for chromium (trivalent) insoluble salts based on a rat chronic feeding study. Male and female rats were administered chromic oxide (Cr_2O_3) baked in bread at dietary levels of 0, 1, 2 or 5% for five days per week for 600 feedings. The RfD was established from a NOAEL of 1,800 g/kg bw average total dose based on a dietary level of 5% Cr_2O_3 (U.S. EPA 1998e, Website). The U.S. EPA (1998e, Website) adjusted the NOAEL to a dose of 1,468 mg/kg bw/d using the equation that follows:

$$NOAEL_{ADJ} = NOAEL \times \frac{1{,}000\ mg}{1\ g} \times \frac{0.6849\ g\ Cr/g\ Cr_2O_3}{600\ feeding\ days} \times \frac{5\ feeding\ days}{7\ days}$$

An uncertainty factor of 100 was applied to the $NOAEL_{ADJ}$ to account for interspecies variability (10-fold) and intra-species variability (10-fold). An additional modifying factor of 10 was applied to reflect database deficiencies including the lack of a study in a non-rodent mammal, lack of unequivocal data evaluating reproductive impacts and concern regarding potential reproductive effects raised by the study of Elbetieha and Al-Hamood (1997).

Given that the RIVM does not provide the details of the study used to derive the oral exposure limit (i.e., duration of exposure, effects observed), this oral limit was not used in the chronic effects assessment of chromium (total). The U.S. EPA oral RfD of 1,500 µg/kg bw/d was used in the chronic effects assessment.

For incorporation in the multiple exposure pathway model, an inhalation bioavailability of 100% (assumed), oral bioavailability of 0.5% (RAIS 2007, Website) and dermal bioavailability of 0.1% (RAIS 2007, Website) were assumed.

3.15 CHROMIUM VI

Chromium VI was assumed to represent 10% of total chromium. The assumption of 10% was originally selected based on the California Air Resources Board (CARB 1985) claim that hexavalent chromium made up between 3 and 8% of total chromium in ambient air. The CARB percentage was rounded from 8% up to 10%. This ratio of total chromium to hexavalent chromium in air was assumed to be consistent throughout all other environmental media (i.e., soils, plants and game).

Although limited information is available on the fraction of hexavalent chromium in soils and biota, recent review of peer-reviewed literature has identified the following with respect to hexavalent chromium in the environment:

- Hexavalent chromium rarely occurs naturally, but is usually produced from anthropogenic (man made) sources (ATSDR 2000).
- Trivalent chromium is the most stable and abundant form in both native and contaminated soil. Hexavalent chromium is transformed to trivalent chromium) during the growing season by micro-organisms and reduction by iron(II), organic matter and sulphide. About 2% of chromium in native soils was found as hexavalent chromium (Fengxiang et al. 2004).
- Chromium is a toxic, nonessential element to plants; hence specific mechanisms for uptake are unavailable. Therefore, uptake of this metal is through carriers used for the uptake of essential metals. Unlike trivalent chromium, hexavalent chromium uptake depends on the expenditure of metabolic energy by the plant. Uptake of hexavalent chromium is probably readily reduced to trivalent chromium in the root, which is the primary (approximately 98%) area where chromium is stored in the plant (ATSDR 2000a; Shanker et al. 2005).
- Trivalent chromium uptake by plants occurs more rapidly than hexavalent chromium (U.S. EPA 1998f, Website).
- In the Priority Substances Assessment List for chromium, Health Canada (CEPA 1994c) states that nearly all of the chromium in soils, sediments and biological tissues is likely present as trivalent chromium.
- Hexavalent chromium that is ingested by mammals is reduced to trivalent chromium before reaching sites of absorption or hexavalent chromium is rapidly reduced to trivalent chromium after penetration of biological membranes (U.S. EPA 1998f, Website; ATSDR 2000a).

Given that the Fengxiang study (Fengxiang et al 2004) indicates that hexavalent chromium represents 2% of total chromium in soils, and that plants and mammals rapidly reduce hexavalent chromium to trivalent chromium, the assumption that hexavalent chromium is 10% of total chromium in all media is considered to be a reasonable worst-case assumption.

3.15.1 Acute Exposure Limit

Table 33 shows the acute inhalation exposure limits for chromium VI as defined by the regulatory agencies.

Table 33 Acute Inhalation Exposure Limits for Chromium VI

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	1	1-hour	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	—	—	OEHHA (2007a)
OMOE	1.5	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The AENV (2007, Website) provides a 1-hour AAQO of 1 µg/m^3, which was adopted from the Texas Natural Resource Conservation Commission. However, no specific basis of derivation was provided for this limit. Thus, the study team is unable to comment on the scientific merit of this limit and it was not included in the current assessment.

The OMOE (2004, 2005a) provides a 24-hour standard for di-, tri- and hexavalent forms of chromium based on the potential for adverse health effects. However, the OMOE (2004) states that the current standard is inadequate for protection of human health given the potential carcinogenicity of hexavalent chromium. The OMOE (2004) proposes to redefine the scope and level of the existing standard for total chromium to include only trivalent and divalent forms. As such, the OMOE's 24-hour standard was not used in the acute effects assessment.

The toxicity search was therefore expanded to include intermediate MRLs and occupational short-term exposure limits (i.e., STEL, Ceiling) (ATSDR 2006a; ACGIH 2006a).

The ATSDR (2000a, 2006a) recommends an intermediate inhalation MRL of 0.001 mg/m^3 for hexavalent chromium particulate compounds based on respiratory effects. Male Wistar rats were exposed to 0, 0.05, 0.1, 0.2 or 0.4 mg Cr(VI)/m^3 as sodium dichromate aerosol particulates for 22 hours per day, seven days per week, for 30 or 90 days (ATSDR 2000a). A Benchmark Concentration (BMC) of 0.016 mg Cr(VI)/m^3 was calculated for alterations in lactate dehydrogenase in the bronchoalveolar lavage fluid using the 90-day exposure data (ATSDR 2000a). The BMC is defined as the 95% lower confidence limit on the concentration corresponding to a 10% relative change in the endpoint compared to the control. The concentration-effect data were adjusted for continuous exposure (i.e., 22 hours/24 hours) and the continuous data fitted to a polynomial mean response regression model to determine the BMCs (ATSDR 2000a). The ATSDR (2000a) converted the BMC to a human equivalent concentration as follows:

$$BMC_{ADJ} = BMC \times RDDR$$

Where:

BMC_{ADJ} = benchmark concentration adjusted for a human (mg/m^3)

BMC = observed benchmark concentration of the study animal ($0.016\ mg/m^3$)

RDDR = multiplicative factor used to adjust observed inhalation particulate exposure concentration of an animal to a predicted inhalation particulate concentration for a human; based on a mass median mean diameter of 0.28 µm and a geometric standard deviation of 1.63, lung effects (thoracic region) (RDDR = 2.1576)

The ATSDR (2000a) applied an uncertainty factor of 30 to the BMC_{ADJ} of $0.034\ mg/m^3$ to account for inter-species variability (3-fold) and intra-species variability (10-fold). An uncertainty factor of 10 was not required for interspecies variability as the BMC was adjusted by the RDDR to determine a human equivalent concentration. The intermediate MRL of 1 $\mu g/m^3$ was conservatively used as the 24-hour exposure limit in the acute effects assessment of chromium (VI).

Use of a subchronic study in the derivation of an acute exposure limit is considered conservative since a higher exposure over a shorter time-period (i.e., acute exposure) presumably could occur without risk of adverse effects.

3.15.2 Chronic Exposure Limit(s)

Table 34 shows the chronic inhalation exposure limits for chromium VI as defined by the regulatory agencies.

Table 34 Chronic Inhalation Exposure Limits for Chromium VI

Regulatory Agency	Value [µg/m³]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	0.00013	RsC	Health Canada (2004b)
RIVM	0.00025	RsC	RIVM (2001)
U.S. EPA	0.0008	RsC	U.S. EPA (1998f, Website)
WHO	0.00025	RsC	WHO (2000, Website)

— = Not available.

The chronic inhalation exposure limit of 0.00013 µg/m^3 was developed by Health Canada (2004b). The RsC was calculated using an inhalation unit risk of 75.8 per mg/m^3, which was derived from a TC_{05} of 0.66 µg/m^3 for hexavalent chromium based on mortality due to lung cancer in a cohort of 332 men employed at a chromate production plant between 1931 and 1937 (CEPA 1994c). The TC_{05} is associated with a 5% increase in lung cancer among plant workers. The inhalation exposure limit corresponds to a lifetime cancer risk of one in 100,000. The RsC of 0.00013 µg/m^3 was used in the chronic effects assessment and is equivalent to an inhaled dose of 0.000029 µg/kg bw/d assuming the average adult weighs 70.7 kg and breaths 15.8 m^3/d (Health Canada 2004a).

Given that chromium VI could persist or bioaccumulate in the environment, an oral exposure limit was required (Table 35).

Table 35 Chronic Oral Exposure Limits for Chromium VI

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	1	RfD	Health Canada (2004b)
RIVM	5	RfD	RIVM (2001)
U.S. EPA	3	RfD	U.S. EPA (1998f, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

Health Canada (2004b) provides a TDI of 1 µg/kg bw/d for chromium (hexavalent). However, no scientific rationale is provided for the derivation of this guideline. As the study team is unable to comment on the scientific merit of this oral exposure limit, it was not used in the current long-term assessment of chromium VI.

The U.S. EPA (1998f, Website) has developed a chronic oral exposure limit of 3 µg/kg bw/d based on a NOAEL of 25 mg/L in a rat drinking water study for which a critical effect was not reported. Based on the body weight of the rat and average daily drinking water consumption, the NOAEL was adjusted to a dose of 2.5 mg/kg bw/d. The U.S. EPA (1998f, Website) applied an uncertainty factor of 300 to the NOAEL to account for interspecies variability (10-fold), intra-species variability (10-fold) and a less-than-lifetime exposure duration (3-fold). An additional modifying factor of 3 was applied to account for concerns raised by another study in which gastrointestinal effects were observed at 20 mg/L. The oral RfD of 3 µg/kg bw/d was used in the chronic effects assessment of chromium (VI).

An inhalation bioavailability of 100% (assumed), oral bioavailability of 2% (RAIS 2007, Website) and dermal bioavailability of 0.1% (RAIS 2007, Website) were assumed for incorporation in the multiple exposure pathway model.

3.16 COBALT

3.16.1 Acute Exposure Limit

Table 36 shows the acute inhalation exposure limits for cobalt as defined by the regulatory agencies.

Table 36 Acute Inhalation Exposure Limits for Cobalt

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	—	—	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	—	—	OEHHA (2007a)
OMOE	0.1	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

Although the OMOE (2005a) provides a 24-hour standard for cobalt, the scientific basis is not provided. As a result, the study team is unable to comment on the scientific merit of this standard and did not use it in the short-term inhalation assessment of cobalt.

An acute criterion or guideline has not been established by any of the other regulatory agencies for cobalt, nor has an inhalation intermediate MRL or short-term occupational limit value (i.e., STEL and Ceiling) (ATSDR 2006a; ACGIH 2006a). Given the absence of an exposure limit, an acute effects assessment was not completed for cobalt. As a result, cobalt was assessed on a chronic basis only.

3.16.2 Chronic Exposure Limit(s)

Table 37 shows the chronic inhalation limits for cobalt as defined by the regulatory agencies.

Table 37 Chronic Inhalation Exposure Limits for Cobalt

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	0.1	RfC	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	0.5	RfC	RIVM (2001)
U.S. EPA	—	—	U.S. EPA (2007, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

The ATSDR (2004, 2006a) provides a chronic inhalation MRL of 0.0001 mg/m^3 for respiratory effects from a cross-sectional study of diamond polishers. Workers from the polishing workshops were divided into a low and high exposure group. Workers from the high-exposure group exhibited reduced lung function and increased spirometric effects compared to controls and the low exposure group. A NOAEL of 0.0053 mg/m^3 was identified for effects on pulmonary function, specifically decreased values upon spirometric examination (ATSDR 2004). The NOAEL was adjusted for intermittent exposure (8 hours/24 hours x 5 days/7 days) to a duration-adjusted NOAEL of 0.0013 mg/m^3. The ATSDR (2004) applied an uncertainty factor of 10 to the duration adjusted NOAEL to account for intra-species variability. The chronic MRL of 0.1 µg/m^3 was used in the chronic effects assessment for cobalt. This value is equivalent to an inhaled dose of 0.022 µg/kg bw/d based on an adult body weight of 70.7 kg and inhalation rate of 15.8 m^3/d (Health Canada 2004a).

Given that cobalt could persist or bioaccumulate in the environment, an oral exposure limit was required (Table 38).

Table 38 Chronic Oral Exposure Limits for Cobalt

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	1.4	RfD	RIVM (2001)
U.S. EPA	—	—	U.S. EPA (2007, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

The RIVM (2001) recommends an oral TDI of 1.4 µg/kg bw/d based on cardiomyopathy after subchronic oral exposure (up to eight months). The lowest LOAEL reported for humans is 0.04 mg/kg. This effect was observed in a small population, which also exhibited adverse effects due to alcohol consumption. The combined effect of exposure to cobalt and alcohol cannot be excluded; therefore, the RIVM (2001) concluded that the lowest effect level will likely be

higher for the general population. Thus, the RIVM (2001) applied an uncertainty factor of 3 to account for intra-species variability. An additional factor of 10 was applied for extrapolation to a NOAEL (RIVM 2001). As the RIVM used a subchronic study to derive a chronic exposure limit, an additional uncertainty factor of 10 should be applied to account for extrapolation from a subchronic to chronic exposure, resulting in an oral exposure limit of 0.14 µg/kg bw/d.

However, given the lack of details regarding the primary study and the combined exposure to cobalt and alcohol, the RIVM oral exposure limit was not used in the current assessment. As there are no other oral exposure limit available for the above regulatory agencies, cobalt was not assessed using the multiple exposure pathway model.

3.17 COPPER

3.17.1 Acute Exposure Limit

Table 39 shows the acute exposure limits for copper as defined by the regulatory agencies.

Table 39 Acute Inhalation Exposure Limits for Copper

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	—	—	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	100	1-hour	OEHHA (2007a)
OMOE	50	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

Although the OMOE (2005a) provides a 24-hour standard for copper, the scientific basis is not provided. As a result, the study team is unable to comment on the scientific merit of this standard and did not use it in the short-term inhalation assessment of copper.

The OEHHA (1999d, 2007a) has developed a 1-hour REL for copper of 100 µg/m^3 that is protective against mild adverse respiratory effects. This REL is based on ACGIH's TLV-TWA of 1 mg/m^3 for copper dust. Exposure to 1 to 3 mg/m^3 of copper dust for an unknown duration resulted in a detectable taste, but no other symptoms. The sweet taste experienced by these workers is consistent with the onset of symptoms of metal fume fever (OEHHA 1999d). An uncertainty factor of 10 was applied to the NOAEL of 1 mg/m^3 to account for

intra-species variability. This 1-hour limit of 100 µg/m^3 was used in the acute effects assessment of copper.

3.17.2 Chronic Exposure Limit(s)

Table 40 shows the chronic inhalation exposure limits for copper as defined by the regulatory agencies.

Table 40 Chronic Inhalation Exposure Limits for Copper

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	1	RfC	RIVM (2001)
U.S. EPA	—	—	U.S. EPA (1991a, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

The RIVM (2001) has developed a Tolerable Concentration in Air (TCA) of 1 µg/m^3 for copper based on a NOAEC of 0.6 mg/m^3 for respiratory and immunological effects. Rabbits were exposed to copper chloride for six hours per day, five days per week for six weeks. The RIVM (2001) applied an uncertainty factor of 100 to the NOAEC to account for interspecies variability (10-fold) and intra-species variability (10-fold). In addition, a correction factor was applied for continuous exposure (6 hours/24 hours x 5 days/7 days). The inhalation limit of 1 µg/m^3 was used in the chronic effects assessment of copper. The RfC is equivalent to an inhaled dose of 0.22 µg/kg bw/d assuming an average adult weighs 70.7 kg and inhales 15.8 m^3/d (Health Canada 2004a).

Given that copper could persist or bioaccumulate in the environment, an oral exposure limit was required (Table 41).

Table 41 Chronic Oral Exposure Limits for Copper

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	30	RfD	Health Canada (2004b)
RIVM	140	RfD	RIVM (2001)
U.S. EPA	—	—	U.S. EPA (1991a, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

Health Canada (2004b) adopted the Health and Welfare Canada (1990) dietary copper intakes that "seem to be adequate and safe" of 30 µg/kg bw/d in adults as its TDI for copper. Health and Welfare Canada (1990) also presents a range of intakes for 3- to 11-year-old children of 50 to 100 µg/kg bw/d. Given that this limit is not health-based, it was not used in the chronic multiple pathway assessment for copper.

The RIVM (2001) has developed a TDI of 140 µg/kg bw/d based on the maximal daily intake of the population. A LOAEL of 4.2 mg/kg bw/d was identified for decreased body weight in mice exposed to copper gluconate. With the application of an uncertainty factor of 1,000 to account for interspecies variability (10-fold), intra-species variability (10-fold) and use of a LOAEL (10-fold), a TDI of 4 µg/kg bw/d would be derived. However, this dose is below the minimum requirements of copper of 20 to 80 µg/kg bw/d. Therefore, the RIVM (2001) applied a margin of safety of 30 to derive a TDI of 140 µg/kg bw/d.

An inhalation bioavailability of 100% (assumed), oral bioavailability of 30% (RAIS 2007, Website) and dermal bioavailability of 0.1% (RAIS 2007, Website) were assumed for incorporation in the multiple exposure pathway model.

3.18 ETHYLBENZENE

3.18.1 Acute Exposure Limit

Table 42 shows the acute inhalation exposure limits for ethylbenzene as defined by the regulatory agencies.

Table 42 Acute Inhalation Exposure Limits for Ethylbenzene

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	2,000	1-hour	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	—	—	OEHHA (2007a)
OMOE	1,000	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The OMOE (2005a) provides a health-based 24-hour standard for ethylbenzene of 1,000 µg/m^3; however, no scientific basis is provided for this standard. As a result, the study team is unable to comment on the scientific merit of this standard and did not use it in the acute effects assessment.

A 1-hour AAQO of 2,000 µg/m^3 has been established by the AENV (2007, Website). This limit was adopted from the TCEQ based on odour perception, but no specific basis was provided. Given that this objective is not health-based, the AENV AAQO was not used in the acute effects assessment.

Thus, the toxicity search was expanded to include intermediate MRLs provided by the ATSDR and short-term occupational limit values (i.e., STEL and Ceiling) (ATSDR 2006a; ACGIH 2006a).

An acute exposure limit of 4,340 µg/m^3 corresponds to the MRL recommended for intermediate inhalation exposure to ethylbenzene by the ATSDR (1999b, 2006a). This MRL was derived from a NOAEL of 97 ppm for developmental effects in Wistar mice following inhalation exposure for seven hours per day, five days per week for three weeks. The ATSDR (1999b) applied an uncertainty factor of 100 to the NOAEL to account for interspecies variability (10-fold) and intra-species variability (10-fold). Use of an intermediate NOAEL when characterizing acute exposure is typically considered conservative, because a higher exposure over a shorter period (i.e., acute exposure) presumably could occur without the risk of adverse effects. The use of this intermediate MRL of 4,340 µg/m^3 as a 24-hour exposure limit is considered appropriate, as the health effects associated with ethylbenzene have been observed to be concentration dependant, rather than duration-dependant.

3.18.2 Chronic Exposure Limit(s)

Table 43 shows the chronic inhalation exposure limits for ethylbenzene as defined by the regulatory agencies.

Table 43 Chronic Inhalation Exposure Limits for Ethylbenzene

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	770	RfC	RIVM (2001)
U.S. EPA	1,000	RfC	U.S. EPA (1991b, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

The RIVM (2001) provides a TCA of 770 µg/m^3 based on kidney and liver effects in rats and mice. A NOAEL of 430 mg/m^3 was identified in the 1992 semi-chronic National Toxicology Program (NTP 1996) study. The RIVM (2001) adjusted the NOAEL for intermittent exposure (6 hours/24 hours x 5 days/7 days) and applied an uncertainty factor of 100 to the duration-adjusted NOAEL of 77 mg/m^3 to account for interspecies variability (10-fold) and intra-species variability (10-fold). An uncertainty factor was not applied to the NOAEL by the RIVM (2001) for use of a subchronic study because a higher NOAEL of 1,075 mg/m^3 was reported in a chronic NTP study.

The U.S. EPA (1991b, Website) assessment of ethylbenzene reports an RfC of 1,000 µg/m^3 based on a NOAEL of 434 mg/m^3 for developmental toxicity in rats and rabbits. Wistar rats and New Zealand white rabbits were exposed to concentrations of 0, 100 or 1,000 ppm (0, 434 or 4,342 mg/m^3) for six to seven hours per day, seven days per week during days 1 to 19 and 1 to 24 of gestation, respectively. According to the U.S. EPA (1991b, Website) methodology, a NOAEL based on developmental effects is not adjusted for intermittent exposure. A $NOAEL_{HEC}$ was calculated assuming a default value of 1.0 since b:a lambda values are unknown for the experimental animal species (a) and humans (h) (U.S. EPA 1991b, Website). An uncertainty factor of 300 was applied to the study $NOAEL_{HEC}$ to account for interspecies variability (3-fold), intra-species variability (10-fold) and the absence of multigenerational reproductive and chronic studies (10-fold). A 3-fold uncertainty factor for interspecies variability was considered appropriate by the U.S. EPA (1991b, Website) since the HEC adjustment addresses the pharmacokinetic component of the extrapolation factor, leaving the pharmacodynamic area of uncertainty.

The TCA provided by the RIVM was not used in the chronic inhalation effects assessment because it is based on a NOAEL from a subchronic study, rather than a NOAEL from a chronic study (i.e., U.S. EPA). As a result, the U.S. EPA RfC of 1,000 µg/m^3 was used in the chronic inhalation effects assessment for ethylbenzene.

Ethylbenzene was not incorporated into the multiple pathway exposure assessment because it did not exceed any of the persistence and bioaccumulation parameters established by Environment Canada (2008, Website). As a result, a chronic oral limit was not required for ethylbenzene.

3.19 ETHYLENE

3.19.1 Acute Exposure Limit

Table 44 shows the acute exposure limits for ethylene as defined by the regulatory agencies.

Table 44 Acute Inhalation Exposure Limits for Ethylene

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	1,200	1-hour	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	—	—	OEHHA (2007a)
OMOE	40	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The OMOE (2005a) provides a 24-hour standard for ethylene which is protective of vegetation and no scientific basis is provided for this standard. Given that this objective is not health-based, the OMOE standard was not used in the acute effects assessment.

A 1-hour AAQO of 1,200 µg/m^3 has been established by the AENV (2003; 2007, Website) based on effects on vegetation. Given that this objective is not health-based, the AENV AAQO was not used in the acute effects assessment.

An acute criterion or guideline has not been established by any of the other regulatory agencies for ethylene, nor has an inhalation intermediate MRL or short-term occupational limit value (i.e., STEL and Ceiling) (ATSDR 2006a; ACGIH 2006a). Thus, ethylene was not assessed in the short-term inhalation assessment. As a result, ethylene was assessed on a chronic basis only.

3.19.2 Chronic Exposure Limit(s)

Table 45 shows the chronic inhalation exposure limits for ethylene as defined by the regulatory agencies.

Table 45 Chronic Inhalation Exposure Limits for Ethylene

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	—	—	RIVM (2001)
U.S. EPA	—	—	U.S. EPA (2007, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

A chronic inhalation exposure limit has not been established by any of the above regulatory agencies for ethylene. Thus, the toxicity search was expanded to include chronic RELs provided by the OEHHA (2007b) and long-term occupational limit values (i.e., TLV-TWAs; ACGIH 2006a).

The ACGIH (2005, 2006a) provides a TLV-TWA for ethylene of 200 ppm (230 mg/m^3) protective of chronic toxicity. The TLV-TWA was developed based on data from a rat study. Fischer 344 rats were exposed to 0, 300, 1,000 or 3,000 ppm ethylene for six hours per day, five days per week for 106 weeks (ACGIH 2005). A comprehensive analysis of tissues (including kidney and nasal turbinates) yielded no effects. The ACGIH (2005) identified a NOAEL of 3,000 ppm and incorporated a suitable uncertainty factor to derive the TLV-TWA.

The TLV-TWA is considered to be protective of a worker repeatedly exposed during an 8-hour workday and a 40-hour workweek (ACGIH 2006a). As such, the TLV-TWA was adjusted from an 8-hour time-weighted average occupational exposure to continuous exposure using the following calculation (U.S. EPA 2002):

$$\text{TLV-TWA}_{ADJ} = \text{TLV-TWA} \times \frac{MV_{ho}}{MV_{h}} \times \frac{Exp_{ho}}{Exp_{h}}$$

Where:

TLV-TWA_{ADJ} = chemical-specific TLV-TWA for chronic exposure via inhalation (mg/m^3)

TLV-TWA = chemical-specific TLV-TWA (230 mg/m^3)

MV_{ho} = amount of air used by a worker during an 8-hour work period (10 m^3/d)

MV_h = amount of air used by an individual in the general population during a day (20 m^3/d)

Exp_{ho} = days per week a worker is exposed (5 days)

Exp_h = days per week an individual in the general population is exposed (7 days)

An uncertainty factor of 10 was applied to the TLV-TWA_{ADJ} of 82 mg/m^3 to account for intra-species variability, resulting in a modified chronic inhalation limit of 8,200 µg/m^3. This modified limit was used in the chronic inhalation effects assessment of ethylene.

Ethylene was not incorporated into the multiple pathway exposure assessment since it did not exceed the persistence and bioaccumulation parameters established by Environment Canada (2008, Website). As a result, a chronic oral exposure limit was not required for ethylene.

3.20 FORMALDEHYDE

3.20.1 Acute Exposure Limit

Table 46 shows the acute inhalation exposure limits for formaldehyde as defined by the regulatory agencies.

Table 46 Acute Inhalation Exposure Limits for Formaldehyde

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	65	1-hour	AENV (2007, Website)
ATSDR	50	2-hour	ATSDR (2006a)
OEHHA	94	1-hour	OEHHA (2007a)
OMOE	65	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The ATSDR (1999c, 2006a) has developed an acute inhalation MRL for formaldehyde of 0.04 ppm (0.05 mg/m^3) based on a LOAEL of 0.4 ppm (0.5 mg/m^3) for nasal and eye irritation. Occupationally exposed patients with skin hypersensitivity to formaldehyde and unexposed (control) patients, all of whom were non-smokers, were separated into two groups. Group 1 included seven male and three female volunteers with skin hypersensitivity to formaldehyde and Group 2 included 11 healthy males with no history of allergic

diseases. Nasal washings were performed in both groups immediately before and after a 2-hour exposure to 0 (placebo) or 0.4 ppm (0.5 mg/m^3) formaldehyde and again four and 18 hours after the exposure period. In both groups, the placebo did not result in any effects on nasal wash cellular contents or symptom score. Exposure to 0.4 ppm (0.5 mg/m^3) formaldehyde showed statistically significant increased average symptom scores compared with average placebo scores, in both groups. As well, eosinophil counts and albumin levels were elevated in both groups. After 18 hours, symptom scores, eosinophil counts and albumin levels were no longer elevated.

A cumulative uncertainty factor of 10 was incorporated by the ATSDR (1999c) to account for intra-species variability (3-fold) and to account for the use of a minimal LOAEL (3-fold). An uncertainty factor of 3 was considered adequately protective of human variability as the symptoms of irritation were observed in a potentially sensitive group of subjects. This 2-hour MRL of 50 µg/m^3 was conservatively used as the 1-hour exposure limit in the acute effects assessment for formaldehyde.

3.20.2 Chronic Exposure Limit(s)

Table 47 shows the chronic inhalation exposure limits for formaldehyde as defined by the regulatory agencies.

Table 47 Chronic Inhalation Exposure Limits for Formaldehyde

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR[(a)]	—	—	ATSDR (2006a)
Health Canada	1.9	RsC	CEPA (2001)
RIVM	—	—	RIVM (2001)
U.S. EPA	0.8	RsC	U.S. EPA (1991c, Website)
WHO	—	—	WHO (2000, Website)

(a) The ATSDR provides a chronic inhalation MRL for formaldehyde that is based on clinical symptoms of mild irritation of the eyes and upper respiratory tract and mild damage to the nasal epithelium and not cancer. Because Health Canada and the U.S. EPA recognize formaldehyde as being a probable human carcinogen, the ATSDR MRL was not considered in the chronic effects assessment.

— = Not available.

Formaldehyde is recognized by Health Canada (CEPA 2001), the U.S. EPA (1991c, Website) and the IARC (2004) as being a probable human carcinogen (Group 1) on the basis of limited or sufficient evidence in humans and sufficient evidence in experimental animals. Health Canada provides a Tumourigenic Concentration (TC_{05}) for formaldehyde of 9.5 mg/m^3 (CEPA 2001). This TC_{05} represents the total intake associated with a 5% increase in incidence of nasal

squamous tumours in rats exposed to formaldehyde for up to 24 months (Monticello et al. 1996). The TC_{05} corresponds to an RsC of 1.9 µg/m^3 that is associated with an increased cancer risk of one in 100,000.

The U.S. EPA (1991c, Website) based its inhalation unit risk on an inhalation study by Kerns et al. (1983) that examined the incidence of squamous cell carcinomas in rats exposed to formaldehyde. In the Kerns et al. (1983) study, Fischer 344 rats and B6C3F1 mice (120 animals/sex/species) were exposed to 0, 2, 5.6 or 14.3 ppm (0, 2.5, 7 or 17.6 mg/m^3) for six hours per day, five days per week for 24 months. Five animals were sacrificed in each exposure group at six and 12 months, while 20 were sacrificed in each exposure group at 18 months (Kerns et al. 1983). The number sacrificed at 24 and 27 months is unclear and the study was terminated at 30 months. Squamous cell carcinomas were seen in the nasal cavities of 51/117 male rats and 52/115 female rats at 14.3 ppm at 30 months. In the 5.6 ppm group, 1/119 male rats and 1/116 female rats showed squamous cell carcinomas of the nasal cavity. No such tumours were seen in the two low dose groups. Incidence rates of polypoid adenomas of the nasal mucosa in rats were as follows: 0 ppm: 1/118 M, 0/114 F; 2 ppm: 4/118 M, 4/118 F; 5.6 ppm: 6/119 M, 0/116 F; 14.3 ppm: 4/117 M, 1/115 F. Among the mice, squamous cell carcinomas were seen in two males at 14.3 ppm. No other lesions were noteworthy.

Using the linearized multi-stage procedure with additional risk the U.S. EPA (1991c, Website) developed an inhalation unit risk of 1.3 x 10^{-5} per µg/m^3, which equates to an RsC of 0.8 µg/m^3 (associated with a one in 100,000 excess cancer risk). The U.S. EPA RsC of 0.8 µg/m^3 was used as the chronic inhalation limit for formaldehyde.

Formaldehyde was not incorporated into the multiple pathway exposure assessment because it did not exceed any of the persistence and bioaccumulation parameters established by Environment Canada (2008, Website). Additionally, formaldehyde tends to remain in the medium to which is discharged, in this case air (CEPA 2001). On this basis, a chronic oral limit was not required for formaldehyde.

3.21 HEXANE GROUP

3.21.1 Acute Exposure Limit

Table 48 shows the acute inhalation exposure limits for the hexane group as defined by the regulatory agencies.

Table 48 Acute Inhalation Exposure Limits for Hexane Group

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	—	—	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	—	—	OEHHA (2007a)
OMOE	7,500	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The OMOE (2005a,b) provides a 24-hour standard of 7,500 µg/m^3 for n-hexane and n-hexane isomers. This standard was developed from a NOAEL of 58 ppm (204 mg/m^3) for polyneuropathy in humans (Sanagi et al. 1980). Workers were exposed to a low concentration of n-hexane and acetone in a tungsten carbide alloys facility for an average of 6.2 years. Significant decreases in mean motor nerve conduction velocities and slowed residual latency of motor conduction of lower extremity were observed. The OMOE (2005b) adjusted the NOAEL from an eight-hour time weighted average for occupational exposure to a value of 73 mg/m^3 for continuous exposure in the general population as follows:

$$NOAEL_{ADJ} = NOAEL \times \frac{MV_{ho}}{MV_h} \times \frac{Exp_{ho}}{Exp_h}$$

Where:

$NOAEL_{ADJ}$ = NOAEL in the human population from continuous exposure (mg/m^3)

NOAEL = NOAEL for discontinuous exposure in an occupational setting (204 mg/m^3)

MV_{ho} = amount of air used by a worker during an 8-hour work period (10 m^3/d)

MV_h = amount of air used by an individual in the general population during a day (20 m^3/d)

Exp_{ho} = days per week a worker is exposed (5 days)

Exp_h = days per week an individual in the general population is exposed (7 days)

An uncertainty factor of 30 was applied to the $NOAEL_{ADJ}$ to account for intra-species variability (10-fold) and potential interaction with other

hydrocarbon solvents in commercial n-hexane (3-fold) (OMOE 2005b). This results in an AAQC of 2,500 µg/m^3 for an n-hexane mixture. The OMOE (2005b) adjusted this value based on the composition of hexane isomers in n-hexane mixture to derive the AACQ of 7,500 µg/m^3 for n hexane and n-hexane isomers. Because the study team does not support the use of chronic toxicity data in the derivation of an acute limit, this acute guideline was not used in the acute effects assessment.

Thus, the toxicity search was expanded to include intermediate MRLs provided by the ATSDR and short-term occupational limit values (i.e., STEL and Ceiling) (ATSDR 2006a; ACGIH 2006a). After reviewing available information and determining that there are no available criteria, guidelines or objectives for hexane with adequate supporting documentation, an acute inhalation limit was developed from the subchronic inhalation BMCL that formed the basis of the U.S. EPA's chronic RfC.

The U.S. EPA (2005a, Website) developed a chronic RfC from a BMCL of 430 mg/m^3 for peripheral neuropathy (decreased mean cell volume at 12 weeks) in a rat subchronic inhalation study. Male Wistar rats (eight/group) were exposed to 0, 500, 1,200 or 3,000 ppm (0, 1,762, 4,230 or 10,574 mg/m^3) n-hexane (more than 99% pure) for 12 hours per day, seven days per week for 16 weeks (Huang et al. 1989). The human equivalent BMCL ($BMCL_{HEC}$) was calculated for an extra respiratory effect of a Category 3 gas. The blood: gas (air) partition coefficient ($H_{b/g}$) value for n-hexane in humans (H) is 0.8, whereas a value of 2.29 has been reported in rats (A) (U.S. EPA 2005a, Website). According to the RfC methodology, where the ratio of animal to human blood: air partition coefficients $[(H_{b/g})_A/(H_{b/g})_H]$ is greater than one, a value of one is used for the ratio by default (U.S. EPA 2005a, Website). Thus, the $BMCL_{HEC}$ is equal to 430 mg/m^3. An uncertainty factor of 100 was applied to the $BMCL_{HEC}$ to account for intra-species variation (10-fold), interspecies variation (3-fold) and database deficiencies (3-fold). The result is a modified limit of 4,300 µg/m^3, which was used as a 1-hour inhalation limit in the acute health effects assessment.

Although the hexane group will be assessed as part of the aliphatic C_2-C_8 group, the modified acute inhalation limit of 4,300 µg/m^3 for hexane is lower then the acute inhalation limit of 100,000 µg/m^3 for the aliphatic C_2-C_8 group. As a result, the hexane group was assessed on an individual basis as well.

3.21.2 Chronic Exposure Limit(s)

Table 49 shows the chronic inhalation exposure limits for the hexane group as defined by the regulatory agencies.

Table 49 Chronic Inhalation Exposure Limits for Hexane Group

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	2,100	RfC	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	—	—	RIVM (2001)
U.S. EPA	700	RfC	U.S. EPA (2005a, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

The U.S. EPA (2005a, Website) developed a chronic RfC of 700 µg/m^3 for neurotoxicity. This RfC is based on a BMCL of 430 mg/m^3 for peripheral neuropathy (decreased mean cell volume at 12 weeks) in a rat subchronic inhalation study. The BMCL was adjusted from intermittent to continuous exposure (12 hours/24 hours) to a concentration of 215 mg/m^3. The human equivalent BMCL ($BMCL_{HEC}$) was calculated for an extra respiratory effect of a Category 3 gas. The blood: gas (air) partition coefficient ($H_{b/g}$) value for n-hexane in humans (H) is 0.8, whereas a value of 2.29 has been reported in rats (A) (U.S. EPA 2005a, Website). According to the RfC methodology, where the ratio of animal to human blood: air partition coefficients $[(H_{b/g})_A/(H_{b/g})_H]$ is greater than one, a value of one is used for the ratio by default (U.S. EPA 2005a, Website). Thus, the $BMCL_{HEC}$ is equal to 215 mg/m^3. The U.S. EPA (2005a, Website) applied an uncertainty factor of 300 to the $BMCL_{HEC}$ to account for interspecies variability (3-fold), intra-species variability (10-fold), extrapolation to chronic exposure from data in a less-than lifetime study (3-fold) and database deficiencies (3-fold).

Application of a full uncertainty factor of 10 for interspecies variation depends on two areas of uncertainty (i.e., toxicokinetic and toxicodynamic uncertainties). In this assessment, the toxicokinetic component is mostly addressed by the determination of a HEC. The toxicodynamic uncertainty is also accounted for to a certain degree by the use of the applied dosimetry method. Thus a partial uncertainty factor of 3 was applied.

A subchronic (16 weeks) study was used for the derivation of the RfC. However, 16 weeks is half of the time required for a newly synthesized neurofilament protein to be transported from the neuronal cell body to the axon terminal in the longest axons of the CNS and the peripheral nervous system of an adult rat (Griffin et al. 1984). Since the lifetime of neurofilaments (target of toxicity of n-hexane) is shorter than the lifetime of an adult rat, extrapolation from subchronic to chronic exposure is not necessary and a partial uncertainty factor of 3 was applied.

The database for n-hexane lacks a developmental neurotoxicity study and a multigeneration reproductive and developmental toxicity study following inhalation exposure to pure n-hexane alone. On this basis, an uncertainty factor of 3 was applied.

This chronic RfC of 700 µg/m^3 was selected as the chronic inhalation limit for n-hexane. The U.S. EPA RfC of 700 µg/m^3 for hexane more conservative than the chronic inhalation limit of 18,400 µg/m^3 for the aliphatic C_2-C_8 group. As a result, the hexane group was assessed on both an individual basis as well as apart of the aliphatic C_5-C_8 group.

The hexane group was not incorporated into the multiple pathway exposure assessment because it did not exceed any of the persistence and bioaccumulation parameters established by Environment Canada (2008, Website). Thus, a chronic oral exposure limit was not required for the assessment of the hexane group.

3.22 HYDROGEN SULPHIDE

3.22.1 Acute Exposure Limit

Table 50 shows the acute inhalation exposure limits for hydrogen sulphide as defined by the regulatory agencies.

Table 50 Acute Inhalation Exposure Limits for Hydrogen Sulphide

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	14 4	1-hour 24-hour	AENV (2007, Website)
ATSDR	98	1-hour	ATSDR (2006a)
OEHHA	42	1-hour	OEHHA (2007a)
OMOE	30	1-hour	OMOE (2005a)
WHO	150	24-hour	WHO (2000, Website)

— = Not available.

The AENV (2007, Website) provides 1-hour and 24-hour AAQOs for hydrogen sulphide of 14 µg/m^3 and 4 µg/m^3, respectively. As well, the OMOE (2005a) recommends a 1-hour AAQC of 30 µg/m^3. All of these guidelines were odour-based rather than health-based and thus were not used in the acute effects assessment for hydrogen sulphide.

The OMOE (2006b) proposes a 24-hour standard of 7 µg/m^3 for hydrogen sulphide based on the U.S. EPA RfC of 2 µg/m^3. The U.S. EPA RfC was derived

from a NOAEL of 13.9 mg/m^3 and converted to a HEC of 0.64 mg/m^3 after adjusting for exposure duration and for differences in the gas respiratory effect in the extrathoracic region between rats and humans (OMOE 2006b). The U.S. EPA applied an uncertainty factor of 300 to account for interspecies variability (3-fold), intra-species variability (10-fold) and subchronic exposure (10-fold) (OMOE 2006b). However, the OMOE (2006b) considered the 10-fold uncertainty factor for extrapolation from a subchronic study to be excessive and used a factor of 3, resulting in a 24-hour limit of 7 µg/m^3.

The OEHHA (1999e, 2007a) provides an acute REL of 42 µg/m^3 based on physiological responses to odour, including headache and nausea. Sixteen individuals were exposed to increasing concentrations of hydrogen sulphide until their odour threshold was reached. The LOAEL was based on the range of odour thresholds of 0.012 to 0.069 ppm that was identified among the individuals. The geometric mean of the odour thresholds (0.03 ppm) was used to develop the acute REL (OEHHA 1999e). An uncertainty factor of 1 was applied to the geometric mean, resulting in an acute REL of 0.03 ppm (42 µg/m^3) (OEHHA 1999e). It is the study team's opinion that these symptoms are not the result of direct systemic toxicity, but rather represent physiological responses triggered by the foul smell of the gas. On this basis, the OEHHA acute REL for hydrogen sulphide was not used in the acute effects assessment because it was based on odour-perception.

The ATSDR (2006a,b) provides an acute inhalation MRL for hydrogen sulphide of 0.07 ppm (98 µg/m^3). This MRL was developed based on a LOAEL of 2 ppm for changes in airway resistance and specific airway conductance in excess of 30% in two of the 10 individuals examined. The test subjects all had bronchial asthma requiring medication for 1 to 13 years, but none of the subjects had severe asthma. The subjects were exposed for a half-hour and their respiratory function in response to a histamine challenge was assessed prior to and following exposure. Although the two subjects showed changes in airway resistance and specific airway conductance, no statistically significant alterations in lung function were observed at this concentration. The ATSDR (2006b) applied a combined uncertainty factor of 30 to account for intra-species variability (3-fold), use of a minimal LOAEL (3-fold) and the lack of studies in children (3-fold). This acute MRL of 98 µg/m^3 was used as a 1-hour exposure limit in the acute effects assessment for hydrogen sulphide.

3.22.2 Chronic Exposure Limit(s)

Table 51 shows the chronic inhalation limits for hydrogen sulphide as defined by the regulatory agencies.

Table 51 Chronic Inhalation Exposure Limits for Hydrogen Sulphide

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	—	—	RIVM (2001)
U.S. EPA	2	RfC	U.S. EPA (2003a, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

The U.S. EPA (2003a, Website) has developed an RfC of 2 µg/m^3 for nasal lesions of the olfactory mucosa. This RfC is based on a NOAEL of 13.9 mg/m^3 for olfactory loss in adult male CD rats following inhalation exposure to hydrogen sulphide for six hours per day, seven days per week for 10 weeks. The U.S. EPA (2003a, Website) adjusted the NOAEL for intermittent exposure (6 hours/24 hours) to a concentration of 3.48 mg/m^3. The $NOAEL_{ADJ}$ was converted to a HEC using the Regional Gas Dosimetry Ratio (RGDR) methodology:

$$RGDR_{ET} = \frac{(V_E/SA_{ET})_A}{(V_E/SA_{ET})_H}$$

$$RGDR_{ET} = \frac{(0.019 \text{ L/min} / 15 \text{ cm}^2)}{(13.8 \text{ L/min} / 200 \text{ cm}^2)}$$

Where:

$RGDR_{ET}$ = regional gas dosimetry ratio in the extrathoracic region

V_E = minute volume in rats $(V_E)_A$ or humans $(V_E)_H$

SA_{ET} = extrathoracic surface area in rats $(SA_{ET})_A$ or humans $(SA_{ET})_H$

The $NOAEL_{ADJ}$ was then multiplied by the $RGDR_{ET}$ of 0.18 to yield a $NOAEL_{HEC}$ of 0.64 mg/m^3, as follows:

$$NOAEL_{HEC} = NOAEL_{ADJ} \times RGDR_{ET}$$

$$NOAEL_{HEC} = 3.48 \text{ mg/m}^3 \times 0.18$$

Finally, the U.S. EPA (2003a, Website) applied an uncertainty factor of 300 to the $NOAEL_{HEC}$ to account for interspecies variability (3-fold), intra-species variability (10-fold) and for subchronic exposure (10-fold). A 3-fold uncertainty

factor was used instead of the 10-fold default value for extrapolation from rats to humans because the calculation of a HEC addresses one of the two areas of uncertainty encompassed in an interspecies uncertainty factor (U.S. EPA 2003a, Website). The HEC adjustment addresses the pharmacokinetic component of the extrapolation factor, leaving the pharmacodynamic area of uncertainty. The U.S. EPA RfC of 2 µg/m^3 was selected as the chronic inhalation limit for hydrogen sulphide.

Hydrogen sulphide was not incorporated into the multiple pathway exposure assessment since it did not exceed any of the persistence and bioaccumulation parameters established by Environment Canada (2008, Website). Thus, a chronic oral exposure limit was not required for hydrogen sulphide.

3.23 LEAD

3.23.1 Acute Exposure Limit

Table 52 shows the acute inhalation exposure limits for lead as defined by the regulatory agencies.

Table 52 Acute Inhalation Exposure Limits for Lead

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	1.5	1-hour	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	—	—	OEHHA (2007a)
OMOE	0.7	30-day	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The AENV (2007, Website) provides an AAQO of 1.5 µg/m^3 for a 1-hour averaging period, which was adopted from the Texas Natural Resource Conservation Commission, but no specific basis is provided. As a result, the study team is unable to comment on the scientific merit of these limits and did not use them in the short-term assessment of lead.

The OMOE (2005a, 2006c) provides a 30-day standard of 0.7 µg/m^3 based on what was considered technically and economically achievable by industry. However, the OMOE (2006c) proposes a revised 30-day standard of 0.3 µg/m^3 given new toxicological and epidemiological information. The 30-day standard was adopted from the California Environmental Protection Agency (Cal EPA) 30-day criterion of 0.3 µg/m^3. The Cal EPA criterion was derived based on a 5%

probability of blood lead levels exceeding 10 µg/dL in children of a defined average subpopulation (OMOE 2006c). The OMOE (2006c) applied a conversion factor of 2.6 to convert the 30-day criterion to one based on a 24-hour averaging period. This factor is supported by empirical measurements and based on the following formula (OMOE 2005c):

$$CF = (t_0 / t_1)^n$$

$$CF = (720 \text{ hours}/24 \text{ hours})^{0.28}$$

Where:

CF = conversion factor (unitless)

t_0 = averaging period that the standard was designed to be used for, expressed in hours (30 days or 720 hours)

t_1 = desired averaging period, expressed in hours (1 day or 24 hours)

n = the OMOE (2005e) recommends a value of 0.28

The 24-hour AAQC of 0.8 µg/m^3 was used in the acute effects assessment of lead.

3.23.2 Chronic Exposure Limit(s)

Table 53 shows the chronic inhalation exposure limits for lead as defined by the regulatory agencies.

Table 53 Chronic Inhalation Exposure Limits for Lead

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	—	—	RIVM (2001)
U.S. EPA	—	—	U.S. EPA (1993b, Website)
WHO	0.5	RfC	WHO (2000, Website)

— = Not available.

An inhalation RfC of 0.5 µg/m^3 is based on the recommendation by the WHO (2000, Website) that the annual average air concentration of lead not exceed 0.05 µg/m^3. This guideline was developed by the WHO (2000, Website) based on the assumption that this air concentration is associated with an upper limit of

non-anthropogenic blood lead level of 10 to 30 µg/L. The critical blood lead level proposed by the WHO (2000, Website) is 100 µg/L, at which haematological and nervous system effects have been observed in adults and children. To protect at least 98% of an exposed population from developing blood lead levels that exceed 100 µg/L, median blood lead levels would not exceed 54 µg/L. Therefore, the guideline of 0.5 µg/m^3 associated with a blood lead level of 30 µg/L is considered protective of children and adults. The inhalation RfC of 0.5 µg/m^3 was used in the chronic effects assessment of lead and is equivalent to an inhaled dose of 0.11 µg/kg bw/d based on an average adult body weight of 70.7 kg and inhalation rate of 15.8 m^3/d (Health Canada 2004a).

Given that lead could persist or bioaccumulate in the environment, an oral exposure limit was required (Table 54).

Table 54 Chronic Oral Exposure Limits for Lead

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	3.6	RfD	Health Canada (2004b)
RIVM	3.6	RfD	RIVM (2001)
U.S. EPA	—	—	U.S. EPA (2004a, Website)
WHO	3.5	RfD	WHO (2003a)

— = Not available.

The RIVM and Health Canada provide oral exposure limits of 3.6 µg/kg bw/d based on the guideline established by the WHO (2003a). The WHO (2003a) provides a TDI of 3.5 µg/kg bw/d developed from the Provisionally Tolerable Weekly Intake (PTWI) of 25 µg/kg bw/d. The PTWI is based on metabolic studies in infants that show that a mean daily intake of 3 to 4 µg/kg body weight is not associated with an increase blood lead level or body burden of lead. Lead retention has been observed at doses of 5 µg/kg body weight or higher. As the WHO guideline of 3.5 µg/kg bw/d forms the basis of both the Health Canada and RIVM RfD values and thus was used in the chronic effects assessment of lead.

For incorporation in the multiple exposure pathway model, an inhalation bioavailability of 100% (assumed), oral bioavailability of 50% (RAIS 2007, Website) and dermal bioavailability of 1% (RAIS 2007, Website) were assumed.

3.24 MANGANESE

3.24.1 Acute Exposure Limit

Table 55 shows the acute inhalation exposure limits for manganese as defined by the regulatory agencies.

Table 55 Acute Inhalation Exposure Limits for Manganese

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	2	1-hour	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	—	—	OEHHA (2007a)
OMOE	2.5	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The AENV (2007, Website) presents a 1-hour limit of 2 µg/m^3, which was adopted from the Texas Natural Resource Conservation Commission. Supporting documentation is not available for the derivation of the Texas value and thus the study team is unable to comment on the scientific merit of this limit and did not use it in the acute effects assessment.

The OMOE (2005a) has developed a 24-hour standard; however, the basis of derivation is not provided. As a result, the study team is unable to comment on the scientific merit of these limits and thus did not use this limit in the acute effects assessment for manganese.

An acute criterion or guideline has not been established by any of the other regulatory agencies for manganese, nor has an intermediate MRL or short-term occupational limit values (i.e., STEL and Ceiling) (ATSDR 2006a; ACGIH 2006a). Given the absence of an exposure limit, an acute effects assessment was not completed for manganese. As a result, manganese was assessed on a chronic basis only (Table 56).

3.24.2 Chronic Exposure Limit(s)

Table 56 Chronic Inhalation Exposure Limits for Manganese

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	0.04	RfC	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	—	—	RIVM (2001)
U.S. EPA	0.05	RfC	U.S. EPA (1993c, Website)
WHO	0.15	RfC	WHO (2000, Website)

— = Not available.

The ATSDR (2000b, 2006a) provides an RfC of 0.04 µg/m^3 for neurological effects in workers exposed in a dry alkaline battery factory (Roels et al. 1992). Workers were exposed an average of 5.3 years (range of 0.2 to 17.7 years) to an average concentration of 215 µg/m^3 respirable dust and 948 µg/m^3 total dust. A control group of age- and area-matched workers that were not occupationally exposed to manganese was included in the study. An audio-verbal short-term memory test, a simple visual reaction time test and three manual tests of hand steadiness, coordination and dexterity were used to measure neurological function. Manganese-exposed workers were significantly worse at performing the neurobehavioural tests than the control group (ATSDR 2000b).

A dose-response curve was developed using the benchmark dose analysis of these data. A lower 95% confidence limit was estimated around the level of manganese exposure expected to result in a 10% response rate (i.e., $BMDL_{10}$). A concentration of 74 µg/m^3 was calculated as the $BMDL_{10}$. The ATSDR (2000b) adjusted the $BMDL_{10}$ to a concentration of 18 µg/m^3 based on discontinuous occupational exposure (8 hours/24 hours x 5 days/7 days) to continuous exposure. An uncertainty factor of 500 was applied to the duration-adjusted $BMDL_{10}$ to account for intra-species variability (10-fold), potential differences in toxicity from different manganese forms (10-fold) and the potentially increased susceptibility in children based on differential pharmacokinetics in the young (5-fold) (ATSDR 2000b). This chronic RfC of 0.04 µg/m^3 was used in the long-term effects assessment of manganese. The inhalation RfC is equivalent to an inhaled dose of 0.0089 µg/kg bw/d based on an average adult body weight of 70.7 kg and inhalation rate of 15.8 m^3/d (Health Canada 2004a).

Given that manganese could persist or bioaccumulate in the environment, an oral exposure limit was required (Table 57).

Table 57 Chronic Oral Exposure Limits for Manganese

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	—	—	RIVM (2001)
U.S. EPA	140	RfD	U.S. EPA (1996a, Website)
WHO	60	RfC	WHO (2004)

— = Not available.

The WHO (2004) provides a TDI of 60 µg/kg bw/d for manganese. The TDI was developed from the upper range of manganese intake in dietary studies (i.e., western and vegetarian diets). This TDI was developed from the upper range of average adult manganese intake in typical Western and vegetarian diets (WHO 2004). The WHO (2004) identified the upper range of 11 mg/d as a NOAEL and applied an adult body weight of 60 kg to derive a dose of 180 mg/kg bw/d. Manganese is not considered to be very toxic to humans given the existence of homeostatic mechanisms and the incidence of adverse health effects at the upper range of dietary intake is negligible. The upper range of the intake (11 mg/day) was identified as a NOAEL, based on the absence of toxic effects (WHO 2004). An uncertainty factor of 3 was also applied by the WHO (2004) to allow for possible increased bioavailability of manganese from water, resulting in a TDI of 60 µg/kg bw/d.

The U.S. EPA (1996a, Website) has developed an oral RfD of 140 µg/kg bw/d based on a NOAEL of 10 mg/d or 0.14 mg/kg bw/d for a 70 kg adult. The NOAEL was derived from composite data from several studies based on Central Nervous System (CNS) effects in humans. An uncertainty factor of one was applied to the NOAEL given that data obtained from large populations consuming normal diets over an extended period of time with no adverse health effects was used (U.S. EPA 1996a, Website). The U.S. EPA (1996a, Website) does recommend a modifying factor of 3 be applied when assessing exposure from drinking water or soil due to concern for possible increased uptake of manganese from water, possible adverse health effects associated with a lifetime exposure through drinking water containing 2 mg/L manganese, possible increased exposure to infants through powdered formula and possible increased absorption and decreased excretion of manganese in neonates. Because the U.S. EPA RfD of 140 µg/kg bw/d is health-based, it was used in the chronic effects assessment of manganese.

An inhalation bioavailability of 100% (assumed), oral bioavailability of 4% (RAIS 2007, Website) and dermal bioavailability of 0.1% (RAIS 2007, Website) were assumed for incorporation in the multiple exposure pathway model.

3.25 MERCURY

3.25.1 Acute Exposure Limit

Table 58 shows the acute inhalation exposure limits for mercury as defined by the regulatory agencies.

Table 58 Acute Inhalation Exposure Limits for Mercury

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	—	—	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	1.8	1-hour	OEHHA (2007a)
OMOE	2	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The OEHHA (1999f, 2007a) has developed an acute REL for mercury (inorganic) of 1.8 µg/m^3, which is protective against severe adverse reproductive and developmental effects. Groups of 12 pregnant rats were exposed by inhalation to 1.8 mg/m^3 of metallic mercury vapour for one hour per day or three hours per day during gestation. The offspring exhibited dose-dependant deficits in behaviour three to seven months after birth in relation to the offspring from controls. The OEHHA (1999f) applied a cumulative uncertainty factor of 1,000 to the LOAEL to account for interspecies variability (10-fold), intra-species variability (10-fold) and the use of a LOAEL (10-fold). Thus, a 1-hour exposure limit of 1.8 µg/m^3 was used in the acute effects assessment of mercury.

3.25.2 Chronic Exposure Limit(s)

Table 59 shows the chronic inhalation exposure limits for mercury as defined by the regulatory agencies.

Table 59 Chronic Inhalation Exposure Limits for Mercury

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	0.2	RfC	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	0.2	RfC	RIVM (2001)
U.S. EPA	0.3	RfC	U.S. EPA (1995b, Website)
WHO	1	RfC	WHO (2000, Website)

— = Not available.

The ATSDR (1999d, 2006a) provides a chronic inhalation MRL of 0.2 µg/m^3 based on an occupational study of male workers, where the critical endpoint evaluated was the occurrence of hand tremors. A LOAEL of 0.026 mg/m^3 was determined by the ATSDR (1999d) from air levels of mercury vapour measured in the plant. The ATSDR (1999d) applied a cumulative uncertainty factor of 100 to the LOAEL to account for intra-species variability (10-fold) and extrapolation of a LOAEL to a NOAEL (10-fold). The RIVM (2001) appears to have adopted the ATSDR's MRL of 0.2 µg/m^3 as its TCA.

The U.S. EPA (1995b, Website) has developed an RfC of 0.3 µg/m^3 for elemental mercury based on a LOAEL of 0.025 mg/m^3 for neurobehavioral effects in occupationally exposed humans in various studies. The observed critical effects included hand tremor, increases in memory disturbance and slight subjective and objective evidence of autonomic dysfunction. The LOAEL was adjusted from an 8-hour TWA occupational exposure to continuous exposure based on the following equation (U.S. EPA 2002):

$$LOAEL_{HEC} = LOAEL \times \frac{MV_{ho}}{MV_h} \times \frac{Exp_{ho}}{Exp_h}$$

Where:

$LOAEL_{HEC}$ = human-equivalent concentration LOAEL adjusted to continuous exposure (mg/m^3)

LOAEL = lowest-observed-adverse-effect-level (0.025 mg/m^3)

MV_{ho} = amount of air used by a worker during an 8-hour work period (10 m^3/d)

MV_h = amount of air used by an individual in the general population during a day (20 m^3/d)

Exp_{ho} = days per week a worker is exposed (5 days)

Exp_h = days per week an individual in the general population is exposed (7 days)

An uncertainty factor of 30 was applied to the $LOAEL_{HEC}$ of 0.009 mg/m^3 by the U.S. EPA (1995b, Website) to account for the protection of sensitive subpopulations and the use of a LOAEL (10-fold) and for database deficiencies (3-fold), particularly lack of developmental and reproductive studies. This inhalation RfC of 0.3 µg/m^3 was used in the long-term assessment of mercury and is equivalent to an inhaled dose of 0.067 µg/kg bw/d based on an average

adult body weight of 70.7 kg and inhalation rate of 15.8 m^3/d (Health Canada 2004a).

Given that mercury could persist or bioaccumulate in the environment, an oral exposure limit was required (Table 60).

Table 60 Chronic Oral Exposure Limits for Mercury

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	0.3	RfD	Health Canada (2004b)
RIVM	2	RfD	RIVM (2001)
U.S. EPA	0.3	RfD	U.S. EPA (1995c, Website)
WHO	2	RfD	WHO (2005a)

— = Not available.

Health Canada (2004b) has established a TDI of 0.3 µg/kg bw/d for mercury; however, supporting documentation is not provided. As a result, the study team is unable to comment on the scientific merit of this limit and thus did not use this TDI in the chronic effects assessment for mercury.

The U.S. EPA (1995c, Website) also provides an oral RfD of 0.3 µg/kg bw/d for mercuric chloride based on a Drinking Water Equivalent Level (DWEL) of 0.01 mg/L for autoimmune effects in rats. The RfD was back calculated from the DWEL, assuming a drinking water consumption rate of 2 L/d and 70 kg body weight. The DWEL was based on three LOAELs of 0.226 mg/kg bw/d, 0.317 mg/kg bw/d and 0.633 mg/kg bw/d from rat subchronic feeding and subcutaneous studies (U.S. EPA 1995c, Website). The U.S. EPA (1995c, Website) applied an uncertainty factor of 1,000 to the lowest LOAEL to account for interspecies variability and sensitive human populations (10-fold), LOAEL to NOAEL conversion (10-fold) and use of subchronic studies (10-fold). The oral RfD of 0.3 µg/kg bw/d was used in the chronic oral assessment of mercury.

For incorporation in the multiple exposure pathway model, an inhalation bioavailability of 100% (assumed), oral bioavailability of 7% (RAIS 2007, Website) and dermal bioavailability of 0.1% (RAIS 2007, Website) were assumed.

3.26 METHYL ETHYL KETONE GROUP

3.26.1 Acute Exposure Limit

Table 61 shows the acute inhalation exposure limits for the methyl ethyl ketone group as defined by the regulatory agencies.

Table 61 Acute Inhalation Exposure Limits for the Methyl Ethyl Ketone Group

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	—	—	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	13,000[(a)]	1-hour	OEHHA (2007a)
OMOE	1,000[(a)] 1,167[(b)]	24-hour 1-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

[(a)] The exposure limit was developed for methyl ethyl ketone.

[(b)] The exposure limit was developed for acetophenone.

— = Not available.

The OMOE (2005a) provides a 1-hour limit of 1,167 µg/m^3 for acetophenone and a 24-hour limit of 1,000 µg/m^3 for methyl ethyl ketone. However, supporting documentation is not available. As a result, the study team is unable to comment on the scientific merit of this limit and did not use it in the acute effects assessment.

The OEHHA (1999g, 2007a) recommends a 1-hour REL of 13,000 µg/m^3 for methyl ethyl ketone based on eye, nose and respiratory irritation. Four human volunteers were exposed to increasing concentrations of methyl ethyl ketone (90 to 270 ppm) in an inhalation chamber for two hours. Eye, nose and throat irritation were reported by the subjects. Lacrimation and sneezing was also observed. The OEHHA (1999g) identified a LOAEL of 270 ppm and applied an uncertainty factor of 60 to account for intra-species variability (10-fold) and use of a minimal LOAEL (6-fold). A time adjustment was not used to extrapolate to a 1-hour concentration due to uncertainties in the precise duration of exposure leading to onset of symptoms (OEHHA 1999g). The acute REL of 13,000 µg/m^3 was used as a 1-hour exposure limit in the short-term effects assessment of the methyl ethyl ketone group.

3.26.2 Chronic Exposure Limit(s)

Table 62 shows the chronic inhalation exposure limits for the methyl ethyl ketone group as defined by the regulatory agencies.

Table 62 Chronic Inhalation Exposure Limits for the Methyl Ethyl Ketone Group

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	—	—	RIVM (2001)
U.S. EPA	5,000	—	U.S. EPA (2003b, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

The U.S. EPA (2003b, Website) provides an inhalation RfC of 5,000 µg/m^3 for methyl ethyl ketone based on developmental toxicity. Pregnant mice were exposed to mean concentrations of 0, 398, 1,010 or 3,020 ppm (0, 1,174, 2,980 or 8,909 mg/m^3) methyl ethyl ketone via inhalation for seven hours per day on gestation days 6 to 15 (Schwetz et al. 1991). Developmental effects observed included decreases in mean fetal weight at 3,020 ppm and a dose-related increase in the incidence of misaligned sternebrae (Schwetz et al. 1991). The results were analyzed by benchmark dose modelling and a Lowest Effective Concentration (LEC) associated with a 5% or 10% extra risk was predicted.

The U.S. EPA (2003b, Website) selected the LEC corresponding to a 10% extra risk of 5,202 mg/m^3 (1,764 ppm) based on the incidence of misaligned sternebrae to derive the RfC. The LEC was adjusted to continuous exposure (7 hours/24 hours) to a LEC_{ADJ} of 1,517 mg/m^3. A HEC was calculated for a gas: respiratory effect. The blood: gas (air) partition coefficient ($H_{b/g}$) was estimated to be 125 in humans and range from 138 to 139 in rats (U.S. EPA 2003b, Website). According to RfC methodology, where the ratio of animal to human blood: air partition coefficients ($(H_{b/g})_A/H(_{b/g})_H$) is greater than one, a default value of one is used (U.S. EPA 2003b, Website). Thus, a LEC_{HEC} of 1,517 mg/m^3 was determined. An uncertainty factor of 300 was applied to the LEC_{HEC} to account for interspecies variability (3-fold), intra-species variability (10-fold) and database deficiencies due to the lack of an inhalation chronic toxicity study and a multigeneration reproductive toxicity study (10-fold). An uncertainty factor of 3 was used for interspecies variability because the calculation of the HEC addressed the pharmacokinetic component of the uncertainty factor. As only the pharmacodynamic area of uncertainty remains, a partial factor of 3 was used (U.S. EPA 2003b, Website). The inhalation RfC of 5,000 µg/m^3 was used in the chronic effects assessment for the methyl ethyl ketone group.

The methyl ethyl ketone group was not incorporated into the multiple pathway exposure assessment since it did not exceed the persistence and bioaccumulation

parameters established by Environment Canada (2008, Website). As a result, a chronic oral exposure limit was not required for the methyl ethyl ketone group.

3.27 METHYL MERCURY

3.27.1 Acute Exposure Limit

The Project will not emit methyl mercury directly into the atmosphere. As such, it was not assessed on an acute basis.

3.27.2 Chronic Exposure Limit(s)

Although the Project will not emit methyl mercury directly to via air, biotransformation of inorganic mercury species to methylated organic species can occur in local waterbodies. As well, plants have some ability to methylate mercury. Methylation is the key step in the entrance of mercury into the food chain (U.S. EPA 2001a). On this basis, methyl mercury was included in the multiple pathway exposure assessment and an oral exposure limit was required (Table 63).

Table 63 Chronic Oral Exposure Limits for Methyl Mercury

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
ATSDR	0.3	RfD	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	0.1	RfD	RIVM (2001)
U.S. EPA	0.1	RfD	U.S. EPA (2001b, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

The U.S. EPA (2001b, Website) provides an oral RfD of 0.1 µg/kg bw/d for developmental neurophysiologic impairment in a number of human epidemiological studies. The RfD is based on a benchmark dose ($BMDL_{05}$) range of 46 to 79 ppb in maternal blood for different neurophysiologic effects in offspring at 7 years of age. This range corresponds to maternal daily intakes of 0.857 to 1.472 µg/kg bw/d. The U.S. EPA (2001b, Website) applied an uncertainty factor of 10 to the $BMDL_{05}$ to account for the pharmacokinetic variability and uncertainty in estimating an ingested mercury dose from cord-blood mercury concentration (3-fold) and pharmacodynamic variability and uncertainty (3-fold). The U.S. EPA RfD of 0.1 µg/kg bw/d was selected as the chronic oral exposure limit for methyl mercury.

For incorporation in the multiple pathway exposure assessment, the oral bioavailability was assumed to be 100% and a dermal bioavailability of 0.001% was used (RAIS 2007, Website).

3.28 MOLYBDENUM

3.28.1 Acute Exposure Limit

Table 64 shows the acute inhalation exposure limits for molybdenum as defined by the regulatory agencies.

Table 64 Acute Inhalation Exposure Limits for Molybdenum

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	—	—	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	—	—	OEHHA (2007a)
OMOE	120	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The OMOE (2005a) provides a 24-hour limit for molybdenum; however, supporting documentation is not available. As a result, the study team is unable to comment on the scientific merit of this limit and did not use it in the acute effects assessment.

An acute criterion or guideline has not been established by any of the other regulatory agencies for molybdenum, nor has an intermediate MRL or short-term occupational limit values (i.e., STEL and Ceiling) (ATSDR 2006a; ACGIH 2006a). Given the absence of an exposure limit, an acute effects assessment was not completed for molybdenum. As a result, molybdenum was assessed on a chronic basis only.

3.28.2 Chronic Exposure Limit(s)

Table 65 shows the chronic inhalation exposure limits for molybdenum as defined by the regulatory agencies.

Table 65 Chronic Inhalation Exposure Limits for Molybdenum

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	12	RfC	RIVM (2001)
U.S. EPA	—	—	U.S. EPA (2007, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

The RIVM (2001) provides an inhalation TCA of 12 µg/m^3 based on a semichronic rat and mouse study. Rats and mice were exposed to molybdenum trioxide via inhalation. Body weight effects were observed at 300 mg/m^3 and a NOAEC of 100 mg/m^3 was identified. The NOAEC was adjusted to continuous exposure to a NOAEC of 12 mg/m^3. The RIVM (2001) applied an uncertainty factor of 1,000 to the duration-adjusted NOAEC to account for interspecies variability (10-fold), intra-species variability (10-fold) and extrapolation from semichronic to chronic exposure (10-fold). The inhalation TCA of 12 µg/m^3 was used in the chronic effects assessment of molybdenum.

Given that molybdenum could persist or bioaccumulate in the environment, an oral exposure limit was required (Table 66).

Table 66 Chronic Oral Exposure Limits for Molybdenum

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	10	RfD	RIVM (2001)
U.S. EPA	5	RfD	U.S. EPA (1993d, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

The U.S. EPA (1993d, Website) provides an oral RfD of 5 µg/kg bw/d based on increased serum uric acid levels in a human dietary exposure study. This value was derived from a cross-sectional human epidemiological study that examined the relationship between dietary molybdenum with serum uric acid and a gout-like condition affected a segment of the adult population within different areas of Armenia. The average daily intake of molybdenum was estimated to range from 0.14 to 0.21 mg/kg-day for an adult (U.S. EPA 1993d, Website). Serum molybdenum was found to be positively correlated with serum uric acid levels. The lower end of the average range was selected as the LOAEL. The U.S. EPA (1993d, Website) applied a cumulative uncertainty factor of 30 to account for the use of a LOAEL (10) and sensitive individuals (3). A full factor of 10 was not

used for intra-species differences due to the large size of the study group. The chronic oral value of 5 µg/kg bw/d was selected for the oral assessment of molybdenum.

For incorporation in the multiple exposure pathway model, an inhalation bioavailability of 100% (assumed), oral bioavailability of 38% (RAIS 2007, Website) and dermal bioavailability of 0.1% (RAIS 2007, Website) were assumed.

3.29 NAPHTHALENE GROUP

3.29.1 Acute Exposure Limit

Table 67 shows the acute inhalation exposure limits for the naphthalene group as defined by the regulatory agencies.

Table 67 Acute Inhalation Exposure Limits for the Naphthalene Group

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	—	—	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	—	—	OEHHA (2007a)
OMOE	22.5	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The OMOE (2005a) has developed an AAQC for naphthalene of 22.5 µg/m^3 based on a 24-hour averaging period. Although the 24-hour criterion is based on health considerations, the specific basis of its derivation remains unknown. Thus, the toxicity search was expanded to include intermediate MRLs provided by the ATSDR and short-term occupational limit values (i.e., STEL and Ceiling) (ATSDR 2006a; ACGIH 2006a).

The ACGIH (1991, 2006a) recommends a STEL of 15 ppm (79 mg/m^3) based on ocular irritation as a result of occupational exposure to naphthalene. The STEL equates to a 15-minute air concentration that should not be exceeded at any time during a workday. The 15-minute STEL can be adjusted to an equivalent 1-hour concentration using a modified Haber's Law:

$$C_{ADJ}^{n} \times T_{ADJ} = C^{n} \times T$$

$$C^{1} \times 60 \text{ minutes} = (79 \text{ mg/m}^3)^{1} \times 15 \text{ minutes}$$

Where:

C_{ADJ} = duration-adjusted concentration

T_{ADJ} = desired time of exposure (60 minutes)

C = concentration of exposure (79 mg/m^3)

T = time of exposure (15 minutes)

n = chemical-specific modification factor designed to account for the toxicity of a chemical being concentration and/or duration dependent. The OEHHA (1999a) recommends using a default *n* value of 1 in the adjustment for less than 1-hour exposure.

Based on the above conversion factor, the STEL was adjusted to a concentration of 20 mg/m^3. A cumulative uncertainty factor of 10 was applied to the duration-adjusted STEL to account for intra-species variability (10-fold). On this basis, the adjusted STEL of 2,000 $\mu g/m^3$ was adopted as a 1-hour exposure limit in the acute effects assessment for the naphthalene group.

3.29.2 Chronic Exposure Limit(s)

Table 68 shows the chronic inhalation exposure limits for naphthalene group as defined by the regulatory agencies.

Table 68 Chronic Inhalation Exposure Limits for the Naphthalene Group

Regulatory Agency	Value [$\mu g/m^3$]	Type	Source
ATSDR	3.7	RfC	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	—	—	RIVM (2001)
U.S. EPA	3	RfC	U.S. EPA (1998a, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

The U.S. EPA (1998a, Website) has derived a chronic inhalation RfC for naphthalene of 3 $\mu g/m^3$. This RfC was estimated from a chronic inhalation mouse study that reported a LOAEL of 9.3 mg/m^3 based on nasal effects including hyperplasia and metaplasia in respiratory and olfactory epithelium (NTP 1992). The U.S. EPA (1998a, Website) incorporated an uncertainty factor of 3,000 to account for interspecies variability (10-fold), sensitive human individuals in the population (10-fold), extrapolation from a NOAEL to a LOAEL (10-fold) and for database uncertainties (3-fold). Database uncertainties included the lack of a two-generation reproductive toxicity study and chronic

inhalation data for other animal species. The U.S. EPA RfC of 3 µg/m^3 was selected as the chronic inhalation limit for the naphthalene group.

Given that the naphthalene group could persist or bioaccumulate in the environment, an oral exposure limit was required (Table 69).

Table 69 Chronic Oral Exposure Limits for the Naphthalene Group

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
ATSDR	600	RfD	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	—	—	RIVM (2001)
U.S. EPA	20	RfD	U.S. EPA (1993e)
WHO	—	—	WHO (2000, Website)

— = Not available.

The ATSDR (2005c, 2006a) has developed an intermediate oral MRL of 600 µg/kg bw/d for naphthalene based upon a reproductive study in female rats from gestational days 6 through 15. A LOAEL of 50 mg/kg was established for signs of clinical toxicity in maternal rats. Uncertainty factors were applied for the use of a minimal LOAEL (3-fold), intra-species variability (3-fold) and inter-species differences (10-fold).

An oral RfD for naphthalene is available from the U.S. EPA (1998a, Website) and is based upon decreased body weights in male rats in a 13-week study. A NOAEL of 100 mg/kg was identified and adjusted to 71 mg/kg due to adjustments for continuous exposure. An uncertainty factor of 3,000 was applied to account for inter-species (10-fold) and intra-species (10-fold) differences, extrapolation from a sub-chronic to a chronic endpoint (10-fold) and a limited toxicological database for oral exposures (3-fold).

Although both values were based upon less-than-chronic exposures, the U.S. EPA RfD incorporated an uncertainty factor to account for this. Thus, the U.S. EPA RfD of 20 µg/kg bw/d was incorporated into the multiple pathway assessment.

Inhalation bioavailability was assumed to be 100%, oral bioavailability 80% and dermal bioavailability 13% based upon RAIS (2007, Website).

3.30 NICKEL

3.30.1 Acute Exposure Limit

Table 70 shows the acute inhalation exposure limits for nickel as defined by the regulatory agencies.

Table 70 Acute Inhalation Exposure Limits for Nickel

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	6	1-hour	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	6	1-hour	OEHHA (2007a)
OMOE	Nickel: 2 Nickel carbonyl: 0.5	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

Although the OMOE (2005a) presents criteria for short-term inhalation exposure to nickel, criteria are based on vegetation and the specific basis of the derivation of this guideline is not provided. Similarly, a 24-hour standard is provided for nickel carbonyl, but the specific basis of its derivation remains unknown. Thus, these guidelines were not used in the acute effects assessment of nickel.

The AENV (2007, Website) provides an AAQO of 6 µg/m^3 for a 1-hour averaging period that was adopted from the OEHHA. The acute REL of 6 µg/m^3 is protective against mild adverse respiratory and immune system effects (OEHHA 1999h, 2007a). Seven volunteer metal plating workers with occupational asthma were exposed via inhalation to 67 µg/m^3 nickel for 30 minutes. A significant (more than 15%) decrease in forced expiratory volume in one second (FEV_1) was observed. The OEHHA (1999h) extrapolated the LOAEL of 67 µg/m^3 to a 1-hour concentration of 33 µg/m^3 using a modified Haber's Law:

$$C_{ADJ}^{n} \times T_{ADJ} = C^{n} \times T$$

$$C^{1} \times 60 \text{ minutes} = (67 \text{ mg/m}^3)^{1} \times 30 \text{ minutes}$$

Where:

C_{ADJ} = duration-adjusted concentration

T_{ADJ} = desired time of exposure (60 minutes)

C = concentration of exposure (37 mg/m^3)

T = time of exposure (30 minutes)

n = chemical-specific modification factor designed to account for the toxicity of a chemical being concentration and/or duration dependent. The OEHHA (1999a) recommends using a default *n* value of 1 in the adjustment for less than 1-hour exposure.

The OEHHA (1999h) applied an uncertainty factor of 6 to the duration-adjusted LOAEL to account for the use of a LOAEL. The modified 1-hour exposure limit of 6 µg/m^3 was used in the acute effects assessment of nickel.

3.30.2 Chronic Exposure Limit(s)

Table 71 shows the chronic exposure limits for nickel as defined by the regulatory agencies.

Table 71 Chronic Inhalation Exposure Limits for Nickel

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	0.09	RfC	ATSDR (2006a)
Health Canada	Nickel oxide: 0.02 Nickel subsulphide: 0.018 Nickel sulphate: 0.0035 Nickel, metallic: 0.018 Nickel, oxidic/sulphidic/soluble: 0.0077 Nickel, soluble: 0.014	RfC RfC RfC RfC RsC RsC	Health Canada (2004b)
RIVM	0.05	RfC	RIVM (2001)
U.S. EPA	Nickel refinery dust: 0.04 Nickel subsulphide: 0.02	RsC	U.S. EPA (1991d, Website, e, Website)
WHO	0.025	RsC	WHO (2000, Website)

— = Not available.

Health Canada (2004b) provides a number of tolerable concentrations for the various forms of nickel; however, there is no scientific rational provided for the development of these guidelines. As a result, the study team is unable to comment on the scientific merit of these limits and thus did not use these tolerable concentrations in the chronic effects assessment for nickel.

The IARC (1997) has classified nickel compounds as carcinogenic to humans (Group 1) and metallic nickel as possibly carcinogenic to humans (Group 2B). Similarly, the U.S. EPA (1991d, Website, e, Website) classifies both nickel refinery dust and nickel subsulphide as human carcinogens and nickel carbonyl

as a probable human carcinogen. Health Canada (2004b) also provides guidelines based on carcinogenic endpoints for both an "oxidic", "sulphidic" and "soluble" nickel (combined) and for a "soluble" nickel. The most conservative exposure limit, which included nickel oxide (a readily available form via inhalation) was selected for the chronic inhalation assessment.

Health Canada (2004b) provides an inhalation unit risk of 1.3 per mg/m^3 for an "oxidic", "sulphidic" and "soluble" nickel (combined), which equates to an RsC of 0.0077 µg/m^3. The unit risk was based on lung cancer mortality data collected from epidemiological studies of exposed workers at INCO mining, smelting and refining operations in Ontario and the Falconbridge refineries in Kristiansand, Norway (CEPA 1994d). The estimated TC_{05}s based on a five percent increase in mortality due to lung cancer ranged from 0.04 to 1.0 mg/m^3, with the unit risk derived from a TC_{05} of 0.04 mg/m^3 (CEPA 1994d; Health Canada 1996). This guideline corresponds to an excess lifetime risk of one in 100,000. The inhalation RsC of 0.0077 µg/m^3 was used in the chronic effects assessment of nickel. The RsC is equivalent to an inhaled dose of 0.0017 µg/kg bw/d based on an average adult body weight of 70.7 kg and inhalation rate of 15.8 m^3/d (Health Canada 2004a).

Given that nickel could persist or bioaccumulate in the environment, an oral exposure limit was required (Table 72).

Table 72 Chronic Oral Exposure Limits for Nickel

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	Nickel chloride: 1.3 Nickel sulphate: 50	RfD RfD	Health Canada (2004b)
RIVM	50	RfD	RIVM (2001)
U.S. EPA	Nickel soluble salts: 20	RfD	U.S. EPA (1996b, Website)
WHO	22	RfD	WHO (2005b)

— = Not available.

Health Canada (2004b) provides TDIs for two forms of nickel; however, there is no scientific rational provided for the development of these guidelines. As a result, the study team is unable to comment on the scientific merit of this limit and thus did not use these TDIs in the chronic effects assessment for nickel.

The U.S. EPA (1996b, Website) recommends an oral RfD of 20 µg/kg bw/d for nickel soluble salts based on a study which showed no adverse effects on body weight and organ weights in rats fed 100 ppm (5 mg/kg bw/d) nickel in their diet over a period of 2 years. The U.S. EPA (1996b, Website) applied an uncertainty factor of 300 to the NOAEL to account for interspecies variability (10-fold),

intra-species variability (10-fold) and to account for inadequacies in the reproductive studies (3-fold).

The WHO (2005b) provides a TDI of 22 µg/kg bw/d for nickel based on developmental effects. A one-generation study was initially conducted to refine the NOAEL range for developmental effects in rats. Based on the results of the one-generation study, exposure levels of 1.0, 2.5, 5.0 and 10 mg/kg bw/d nickel sulphate hexahydrate were administered via gavage to five groups of male and female rats in a two-generation study (WHO 2005b). A NOAEL of 10 mg/kg bw/d was determined for post-implantation/perinatal lethality, which is equivalent to a NOAEL of 2.2 mg/kg bw/d for nickel. The WHO (2005b) applied an uncertainty factor of 100 to the NOAEL to account for interspecies variability (10-fold) and intra-species variability (10-fold).

Due to the fact that the U.S. EPA had low confidence in the study used to determine their guideline, as well as that the WHO conducted a more recent review of nickel and thus used a more recent study which they considered to be well-conducted, the WHO oral exposure limit of 22 µg/kg bw/d was used in the current assessment.

For incorporation in the multiple exposure pathway model, an inhalation bioavailability of 100% (assumed), oral bioavailability of 27% (RAIS 2007, Website) and dermal bioavailability of 0.1% (RAIS 2007, Website) were assumed.

3.31 NITROGEN DIOXIDE

Chemicals of potential concern that are governed and defined at the federal government level in the form of either National Ambient Air Quality Objectives (NAAQOs) or as a Canada-Wide Standard (CWS) were not subjected to the typical screening process. Instead, the AAQOs adopted by the AENV (2007, Website) from Health Canada were given priority. Nitrogen dioxide is one of these chemicals.

3.31.1 Acute Exposure Limit

The exposure limits used for the acute effects assessment of nitrogen dioxide were based on AENV's AAQOs (AENV 2007, Website). These include a 1-hour objective of 400 µg/m^3 and a 24-hour objective of 200 µg/m^3. These AAQOs were adopted from the Health Canada's NAAQOs for nitrogen dioxide. The NAAQOs are developed in three tiers: maximum desirable, acceptable and tolerable objectives. The Alberta objectives are based on the maximum

acceptable levels, as maximum desirable NAAQOs (i.e., the lowest objectives) have not been developed for nitrogen dioxide on an acute-basis. These NAAQOs are health-based and rely on controlled studies of the most sensitive population (i.e., asthmatics) to nitrogen dioxide.

Using the above objectives and guidelines, the acute assessment for nitrogen dioxide was completed on a 1-hour and 24-hour basis.

3.31.2 Chronic Exposure Limit(s)

The chronic exposure limit used for the assessment of nitrogen dioxide concentrations in air was based on AENV's AAQO of 60 µg/m^3 (AENV 2007, Website). This guideline was adopted from Health Canada's NAAQO for nitrogen dioxide based on an annual averaging time. The NAAQOs are developed in three tiers: maximum desirable, acceptable and tolerable objectives. The maximum desirable level (i.e., the lowest objective) was adopted as the annual objective in Alberta. This objective is health-based and relies on controlled studies of the most sensitive population (i.e., asthmatics) to nitrogen dioxide.

Nitrogen dioxide was assessed only for the inhalation route of exposure as the principal health effects are strictly related to inhalation.

3.32 PARTICULATE MATTER ($PM_{2.5}$)

Chemicals of potential concern that are governed and defined at the federal government level in the form of either National Ambient Air Quality Objectives (NAAQOs) or as a Canada-Wide Standard (CWS) were not subjected to the typical screening process. Instead, the AAQOs adopted by the AENV (2007, Website) from Health Canada were given priority. Particulate matter (as $PM_{2.5}$) is one of these chemicals.

Particulate Matter (PM) is the generic term applied to a broad class of chemically and physically diverse substances that exist as discrete particles (liquid droplets or solids) over a range of sizes. Particles less than 2.5 micrometers (less than 2.5 µm) are called "fine" particles (i.e., $PM_{2.5}$), while those larger than 2.5 µm but smaller than 10 µm are known as "coarse" particles (i.e., $PM_{2.5-10}$). When inhaled, these particles can reach the deepest regions of the lungs (U.S. EPA 2006, Website).

A significant amount of research has been and is being conducted on the health effects associated with both fine and coarse PM in the ambient air. Short-term

exposure to ambient PM in numerous urban areas has been associated with a range of health outcomes including:

- premature death in people with heart and lung disease;
- non-fatal heart attacks;
- respiratory and cardiovascular hospitalizations;
- lung function changes;
- adverse respiratory symptoms (e.g., cough, wheeze);
- aggravated asthma; and
- irregular heartbeats (U.S. EPA 2004c).

Long-term exposure to fine particles ($PM_{2.5}$) has been associated in some studies with cardiovascular and lung cancer mortality, effects on lung function and increases in respiratory symptoms (Brauer et al. 2002; Gauderman et al. 2004; Krewski et al. 2003, 2005a,b; Pope et al. 2002, 2004a,b). These associations do not appear to be explainable by other factors (e.g., weather and other compounds) and after careful review of the evidence, most scientists agree that these seem to be causal in nature (Samet et al. 2000 (reanalyzed in Health Effects Institute (HEI) 2003); CEPA 2000b; U.S. EPA 2004b,c). This presents a difficult problem because PM is ubiquitous in the environment and sources are both natural and anthropogenic. Populations identified as being more sensitive to the adverse health effects of PM include individuals with existing respiratory or cardiovascular disease, the elderly, children and asthmatics (U.S. EPA 2004b,c).

Existing epidemiological studies on large populations have been unable to identify a threshold concentration below which ambient PM has no effect on health. It is likely that thresholds for specific responses exist for specific individuals, but these may vary markedly in the general population resulting in such a wide range in susceptibility that the identification of an explicit threshold for the general population may be impossible (WHO 2003b). The U.S. EPA has noted that a convincing mathematical demonstration of a clear threshold in the population studies available is both complex and difficult to verify. They concluded that available evidence does not support or refute the existence of thresholds for the effects of PM on mortality across the range of concentrations in the studies (U.S. EPA 2004c).

The health impacts from exposure to PM are generally small in terms of measurable or relative risk. For example, the magnitude of the effect of PM exposure is much smaller than the effects of tobacco smoke (HEI 2001). However, because exposure to PM is widespread, the public health impact of

increased air pollution (and in turn PM) can be significant. A recent large study of hospital admissions in 204 counties across the United States found a 10 $\mu g/m^3$ same day increase in $PM_{2.5}$ was associated with 0.5 to 2% increased hospital admissions for cardiovascular and respiratory diseases by region (Dominici et al. 2006). Variation in risk across regions was also found. For example, positive associations with cardiovascular hospital admissions were found only in the Eastern region of the United States. By contrast, relative risk estimates for respiratory tract infections were larger in the Western region (Dominici et al. 2006).

The emphasis of PM research has been shifting in recent years to address the many unanswered questions about how particles cause the health effects observed in epidemiological studies. Primary among these are questions related to a) the biological mechanisms responsible for the effects observed and; b) the types and sources of particles most likely causing the effects observed. At present, PM standards are based solely on size fraction (e.g., $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$) but future standards could target the particle components or characteristics that are most toxic.

The primary biological mechanisms thought to underlie the reported health effects from ambient PM include oxidative stress and pulmonary or systemic inflammation (U.S. National Research Council (U.S. NRC) 2004). Clinical and toxicological studies suggest that PM exposure is associated with increased airway hyperactivity, oxidative stress, inflammation, arrhythmias, atherosclerosis, heart rate variability, blood pressure and changes in blood characteristics (e.g., levels of C-reactive protein, fibrinogen, blood viscosity). This provides the important biological plausibility required to explain the morbidity and mortality observed in susceptible individuals in epidemiological studies. However, uncertainty remains in the degree to which toxicological findings from in vitro systems and high dose animal studies apply to real world human exposures, which are often orders of magnitude lower (U.S. NRC 2004). The U.S. NRC states that: The findings from the clinical, animal and in vitro experimental work have often not addressed dose-response relationships, which may provide critical insights into the relevance of the experimental findings for interpreting epidemiological research (U.S. NRC 2004). Many studies also used a non-physiologic route of exposure such as intratracheal instillation, which the U.S. EPA (2004c) notes can result in very high individual cellular concentrations, requiring much caution in the extrapolation of findings.

Determining the characteristics of PM that are associated with adverse health effects is challenging. PM in ambient air is a complex mixture that varies in size and chemical composition, as well as varying spatially and temporally. Different types of particles may cause different effects with different time courses and

perhaps only in susceptible individuals. The interaction between PM and gaseous co-pollutants adds additional complexity because in ambient air pollution, a number of pollutants tend to co-occur and have strong inter-relationships with each other (e.g., PM, sulphur dioxide [SO_2], nitrogen dioxide [NO_2], carbon monoxide [CO] and ozone [O_3]) as well as different levels of measurement error (Peel et al. 2005; U.S. EPA 2004c). As a result it is difficult to attribute the effects of air pollution as a mixture to any one of these particular pollutants. A pollutant that exhibits a relatively strong association in a multi-pollutant model may be acting as a surrogate for an unmeasured or poorly measured pollutant (Metzger et al. 2004). Several investigators have noted that the effects observed in their studies are likely due to the mixture of air pollutants and not just one component (Chen et al. 2004; Goldberg et al. 2006).

Considerable research effort has gone into understanding the PM sources, components and size fractions likely to be responsible for the health effects observed in epidemiology studies. Characteristics that have been found to contribute to toxicity include: metal content, presence of polycyclic aromatic hydrocarbons and other organic components, endotoxin content and small (less than 2.5 μm) and extremely small (less than 0.1 μm) size (CAFÉ 2004, Website).

Several studies using factor analyses indicate that combustion particles in the fine fraction but not fine crustal particles are associated with increased mortality (Laden et al. 2000; Schwartz et al. 1999; Mar et al. 2000; Tsai et al. 2000; Ozkaynak et al. 1996; Janssen et al. 2002). Crustal particles (also referred to as geological particles) are products of the natural abrasion of the earth's crust and are mainly mechanically generated from agriculture, mining, construction, road dust and related sources. Particles associated with motor vehicle emissions stand out clearly as a source category associated with mortality in the factor analyses studies, but associations with an oil combustion factor, a regional sulphate factor and a source category related to vegetative burning have also been identified. Regional sulphate is highly correlated with $PM_{2.5}$, however, so it may be acting as a surrogate for $PM_{2.5}$ (U.S. EPA 2004c).

Several studies have reported significant associations between adverse health effects and either traffic density or close proximity to major roads, including total and cardiopulmonary mortality, heart attacks and adverse respiratory health effects (Brauer et al. 2002; Finkelstein et al. 2004; Hoek et al. 2002; Kim et al. 2004; Lipfert et al. 2006; Tonne et al. 2006; Venn et al. 2001). For example, in Hamilton, Ontario, living within 100 metres of a freeway or 50 metres of a major urban road was associated with increased all cause mortality (RR = 1.18; 1.02-1.38) (Finkelstein et al. 2004). The mortality rate advancement associated with residence near a major road was 2.5 years in this study, which is similar to that associated with chronic respiratory and pulmonary diseases and diabetes. In

a study of 70,000 male US veterans, Lipfert et al. (2006) reported that county-level traffic density was a better predictor of mortality than with ambient $PM_{2.5}$ levels. In multi-pollutant models including traffic density, the association with $PM_{2.5}$ was reduced and lost statistical significance (Lipfert et al. 2006). Another study reported that time spent in traffic (e.g., cars, public transport, bicycles) two hours prior was much more strongly associated with induction of nonfatal Myocardial Infarctions (MIs) than any of the air pollutants measured at a central monitoring site (Peters et al. 2005).

Future epidemiological studies and studies currently in progress should provide important information on the relative role of various PM size fractions and components in adverse health effects. A collection of studies in Atlanta is using extensive air quality data, including detailed PM composition and size fraction information from a monitoring station operated by the Aerosol Research and Inhalation Epidemiology Study (ARIES). Parameters measured include several gases and many PM components, including total metals, water-soluble metals, Organic Carbon (OC) and elemental carbon, sulphates, nitrates, several speciated hydrocarbons and polar VOCs (Metzger et al. 2004; Peel et al. 2005). Time series studies using ARIES data that examined associations with emergency department visits suggest the strongest and most consistent associations are with traffic related pollutants such as NO_2, CO, $PM_{2.5}$, OC, elemental carbon and oxygenated carbons (Metzger et al. 2004; Peel et al. 2005). Consistent associations with sulphates were not demonstrated.

A recent time-series analysis of PM in California indicated that ambient concentrations of several constituents of $PM_{2.5}$ were associated with daily mortality, specifically elemental carbon, OC, nitrates, copper, potassium, titanium and zinc (Ostro et al. 2006). Many of these constituents were associated with higher relative risks than $PM_{2.5}$ mass. The authors noted that their results support the hypothesis that pollution from motor vehicles and other sources of combustion may be of particular concern (Ostro et al. 2006).

Seagrave et al. (2006) examined the lung toxicity of ambient PM from various U.S. sites with different contributing sources and reported on the relationship between composition and effects. Summer and winter samples from each site were collected for toxicity testing, chemical analysis and source apportionment. After instillation into rat lungs, general toxicity, acute cytotoxicity and inflammation were assessed. The results support the concept that $PM_{2.5}$ composition affects its toxicity (Seagrave et al. 2006). Source apportionment suggested that the most potent samples were those with the largest contributions from diesel and gasoline exhaust. Wood burning was only weakly correlated with toxicity end points, while sulphate (SO_4^{2-}), secondary organic aerosols, meat

cooking and vegetation burning were not correlated with the biological responses.

Untangling the relationships among components of mixtures of PM requires a sophisticated integration of air quality and health research and a systematic study of PM components (Samet et al. 2005). The Health Effects Institute (HEI) has noted that a systematic approach to these topics will generate more specific PM standards and ones that target the types and inventories of particles most likely to contribute to health effects. Such a research initiative may lead to the identification of critical PM sources, enabling industry-specific guidance for control of those specific PM components that have been attributed with the greatest fraction of risk to health (HEI 2005, Website).

3.32.1 Acute and Chronic Exposure Limits

The Scientific Assessment Document (Part 1) of The National Ambient Air Quality Objectives for Particulate Matter prepared by the CEPA/FPAC Working Group on Air Quality Objectives and Guidelines concluded that both the mortality and hospitalization studies support the identification of 15 $\mu g/m^3$ averaged over 24 hours as the reference level for $PM_{2.5}$ (CEPA/FPAC 1999). The reference level was considered an estimate of the lowest ambient particulate matter level at which statistically significant increases in health responses can be detected based on data available up to 1996. It was derived based on the average 24-hour concentrations measured in the cities where these effects were found. The CEPA/FPAC (1999) Working Group states that reference levels should not be interpreted as thresholds of effects, or levels at which impacts do not occur. They are defined under Canada's National Ambient Air Quality Objectives as levels above which there are demonstrated effects on human health and/or the environment (CEPA/FPAC 1999).

A Canada-Wide Standard (CWS) of 30 $\mu g/m^3$ $PM_{2.5}$ averaged over 24 hours was developed by the CCME under the auspices of the Canadian Environmental Protection Agency (CEPA) (CCME 2000b). Under this standard, the government is committed to reduce levels of $PM_{2.5}$ significantly by 2010. Achievement of this standard is based on the 24-hour 98^{th} percentile of the ambient measurement annually, measured over three consecutive years. The CWS is considered to be an important step towards the long-term goal of reducing the health risks of $PM_{2.5}$. It represents a balance between achieving the best health and environmental protection possible and the feasibility and costs of reducing pollutant emissions that contribute to $PM_{2.5}$ in ambient air.

The California Air Resources Board (CARB) has identified an air quality annual average standard for $PM_{2.5}$ of 12 $\mu g/m^3$ (CARB 2002a, Website, b). This

recommended arithmetic mean value was "based on a growing body of epidemiological and toxicological studies showing significant toxicity (resulting in mortality and morbidity) related to exposure to fine particles". Similar to the CEPA/FPAC reference level, the value was derived mainly based on the average 24-hour concentrations in cities where statistically significant increases in health responses were detected. The CARB Staff report recommendation was adopted by the State of California as an ambient air quality standard in June of 2002.

In 1997, the U.S. EPA first set National Ambient Air Quality Standards (NAAQS) for fine particles. Two primary $PM_{2.5}$ standards were set: an annual standard of 15 $\mu g/m^3$ to protect against health effects caused by exposures ranging from days to years and a 24-hour standard of 65 $\mu g/m^3$ to provide additional protection on days with high peak $PM_{2.5}$ concentrations. In September 2006, the U.S. EPA issued a new suite of standards to better protect public health from particle pollution. The revised NAAQS for $PM_{2.5}$ reduced the 24-hour standard from 65 to 35 $\mu g/m^3$ and retained the annual standard of 15 $\mu g/m^3$ (U.S. EPA 2006, Website). The 24-hour standard is based on the 98th percentile annual measurement, averaged over 3 years, while the annual standard is met when the 3-year average of the annual average $PM_{2.5}$ concentration is less than or equal to 15 $\mu g/m^3$. The U.S. EPA (2006, Website) also retained the existing 24-hour NAAQS for PM_{10} of 150 $\mu g/m^3$ and revoked the annual PM_{10} standard of 50 $\mu g/m^3$.

The final NAAQSs were selected by the U.S. EPA after completing an extensive review of thousands of scientific studies on the impact of fine and course particles on public health. The criteria document (i.e., the review) and the staff paper containing the U.S. EPA's recommendations on the range of alternative standards that should be considered, received extensive review by representatives of the scientific community, industry and public interest groups as well as the Clean Air Scientific Advisory Committee (CASAC) – a group of independent scientific and technical experts established by Congress (U.S. EPA 2006, Website).

It is worth noting that the final annual standard for $PM_{2.5}$ selected by the U.S. EPA does not reflect the advice of the CASAC PM panel, who recommended a 24-hour standard in the range of 30 to 35 $\mu g/m^3$ and an annual standard in the range of 13 to 14 $\mu g/m^3$ (CASAC 2006). They noted that clear and convincing scientific evidence as well as the U.S. EPA's own risk analyses (U.S. EPA 2005c) indicated health risks at the current annual standard of 15 $\mu g/m^3$. Risk analyses indicated that uncertainties increase rapidly below an annual level of 13 $\mu g/m^3$ and that was the basis for CASAC's recommendation of 13 $\mu g/m^3$ as the lower bound for the annual $PM_{2.5}$ standard. The provisions do not require U.S. EPA standards to be set at a zero risk level but rather at a level that avoids

unacceptable risks to public health. However, previously the U.S. EPA has accepted CASAC's advice with respect to NAAQS decisions (CASAC 2006).

The WHO (2005c) suggests that PM guidelines cannot ensure the complete protection against adverse health effects because thresholds have not been identified and it is unlikely that any PM guideline will provide adequate protection for every individual against all possible adverse effects. Instead, guidelines need to achieve the lowest concentrations possible considering local constraints, capabilities and public health priorities.

With respect to air quality guidelines for $PM_{2.5}$, the WHO recommends an annual average of 10 $\mu g/m^3$ and a daily 99th percentile of 25 $\mu g/m^3$ for the protection of public health. The WHO (2005c) suggests the annual average should take precedence over the daily guideline because at low levels there is less concern for episodic excursions. The annual average guideline is based on long-term exposure studies using the American Cancer Society (ACS) data (Pope et al. 2002) and Harvard Six-Cities data (Dockery et al. 1993). The studies reported a robust association between PM exposure and mortality. Historical mean $PM_{2.5}$ concentrations across cities in these two studies were 18 and 20 $\mu g/m^3$, respectively but average concentrations in individual cities were as low 11 $\mu g/m^3$ over the period of study. An annual mean guideline concentration of 10 $\mu g/m^3$ was therefore noted to be below the mean for most likely effects (WHO 2005c). However, both the WHO (2005c) and the U.S. EPA (2005c) note that statistical uncertainties in the risk estimates become apparent at concentrations of about 13 $\mu g/m^3$, below which confidence bounds significantly widen, indicating the possibility of an effects threshold. In their staff paper, the U.S. EPA (2005c) noted that an annual standard of 12 $\mu g/m^3$ would be precautionary, but a standard set below the range of 12 to 15 $\mu g/m^3$ would be highly precautionary, "giving little weight to the remaining uncertainties in the broader body of evidence, including other long-term exposure studies that provide far more inconsistent results".

It is apparent that the health protection afforded by the reference level for $PM_{2.5}$ of 15 $\mu g/m^3$ that was established by the CEPA/FPAC in 1999 should be considered generally equivalent to the intended or effective health protection of the Ambient Air Standard of California (12 $\mu g/m^3$), the annual NAAQ standard retained by the U.S. EPA (15 $\mu g/m^3$) or the new WHO annual guideline of 10 $\mu g/m^3$ $PM_{2.5}$.

The short-term value represented by the CWS of 30 $\mu g/m^3$ is analogous to the new 24 hour NAAQS identified by U.S. EPA of 35 $\mu g/m^3$, which was determined to better protect the public from the health effects associated with short-term fine particle exposures. The CWS is within the range set by the WHO annual

guideline for $PM_{2.5}$ of 10 µg/m^3 and the U.S. EPA NAAQS of 35 µg/m^3. CARB refrained from setting a 24-hour standard in 2002 and has deferred a decision on this matter (CARB 2002b).

For the current assessment, predicted 24-hour $PM_{2.5}$ concentrations are compared to the CWS of 30 µg/m^3, which falls within the range of recent standards recommended by the WHO and the U.S. EPA. Predicted annual average concentrations were compared against the CARB annual standard of 12 µg/m^3, which also falls within the range of standards recommended by the WHO and the U.S. EPA. The choice of standards in the middle of the range of available guidelines or standards respects both the need to be conservative and the uncertainty which still remains regarding the types of PM that are most toxic and the existence of a threshold for PM-associated adverse effects.

3.33 SELENIUM

3.33.1 Acute Exposure Limit

Table 73 shows the acute inhalation exposure limits for selenium as defined by the regulatory agencies.

Table 73 Acute Inhalation Exposure Limits for Selenium

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	—	—	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	—	—	OEHHA (2007a)
OMOE	10	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The OMOE (2005a) provides a 24-hour limit for selenium; however, supporting documentation is not available. As a result, the study team is unable to comment on the scientific merit of this limit and did not use it in the acute effects assessment.

An acute criterion or guideline has not been established by any of the other regulatory agencies, nor has an intermediate MRL or short-term occupational exposure value (i.e., STEL and Ceiling) (ATSDR 2006a; ACGIH 2006a). As such, selenium was assessed on a chronic basis only.

3.33.2 Chronic Exposure Limit(s)

Table 74 shows the chronic inhalation exposure limits for selenium as defined by the regulatory agencies.

Table 74 Chronic Inhalation Exposure Limits for Selenium

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	—	—	RIVM (2001)
U.S. EPA	—	—	U.S. EPA (2007, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

A chronic inhalation criterion or guideline is not provided by any of the above regulatory agencies for selenium. Consequently, the toxicity search was expanded to include chronic RELs by the OEHHA (2007b) and occupational exposure limits (ACGIH 2006a).

The OEHHA (2001, 2007b) has developed a chronic REL of 20 µg/m^3 based on the oral exposure limit of 5.0 µg/kg bw/d recommended by the U.S. EPA (1991f, Website). The exposure limit is based on a NOAEL of 0.015 mg/kg bw/d for clinical selenosis (liver, blood, skin and CNS effects) observed in a human epidemiological study of 400 individuals from China (OEHHA 2001). A blood selenium concentration of 1.0 mg/L, at which selenosis was not observed, corresponded to a NOAEL of 0.85 mg/d, which was adjusted by the study author for an average adult body weight of 55 kg. The OEHHA (2001) derived the reference level through route-to-route extrapolation of the RfD using an inhalation extrapolation factor of 3,500 µg/m^3.

The ACGIH (1991, 2006a) provides a TLV-TWA occupational exposure limit of 0.2 mg/m^3 for selenium compounds to prevent systemic toxicity and minimize the potential for ocular and upper respiratory tract irritation. The TLV-TWA was developed based on a review of extensive literature regarding the clinical toxicology and the incidence of selenium poisoning as a result of ingestion of seleniferous grains and other foodstuffs. It was also based on reports that did not identify any disabling chronic diseases or death from industrial exposure. The TLV-TWA appears to be derived from the lowest measured air concentration of 0.2 mg/m^3 collected in a selenium rectifier plant where symptoms of selenosis were recorded, including a garlic odour on the breath, skin rashes, gastrointestinal distress, metallic taste and various psychological effects. These findings were consistent with chronic selenosis symptoms reported from oral

exposure. The TLV-TWA was adjusted from an 8-hour occupational exposure to continuous exposure based on the following equation (U.S. EPA 2002):

$$\text{TLV-TWA}_{ADJ} = \text{TLV-TWA} \times \frac{MV_{ho}}{MV_h} \times \frac{Exp_{ho}}{Exp_h}$$

Where:

TLV-TWA_{ADJ} = chemical-specific TLV-TWA for chronic exposure via inhalation (mg/m^3)

TLV-TWA = chemical-specific TLV-TWA (0.2 mg/m^3)

MV_{ho} = amount of air used by a worker during an 8-hour work period (10 m^3/d)

MV_h = amount of air used by an individual in the general population during a day (20 m^3/d)

Exp_{ho} = days per week a worker is exposed (5 days)

Exp_h = days per week an individual in the general population is exposed (7 days)

An uncertainty factor of 100 was applied to the TLV-TWA_{ADJ} of 0.07 mg/m^3 to account for intra-species variability (10-fold) and apparent use of a LOAEL (10-fold). This results in a chronic exposure limit of 0.7 $\mu g/m^3$.

As the OEHHA chronic inhalation REL was derived from an oral exposure limit, it was not used in the current assessment. The ACGIH provides a limit based on a chronic endpoint associated with inhalation exposure and therefore was considered more appropriate. Thus, the chronic exposure limit of 0.7 $\mu g/m^3$ was used in the health risk assessment. This inhalation REL is equivalent to an inhaled dose of 0.16 µg/kg bw/d based on an average adult body weight of 70.7 kg and inhalation rate of 15.8 m^3/d (Health Canada 2004a).

Given that selenium could persist or bioaccumulate in the environment, an oral exposure limit was required (Table 75).

Table 75 Chronic Oral Exposure Limits for Selenium

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
ATSDR	5	RfD	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	—	—	RIVM (2001)
U.S. EPA	5	RfD	U.S. EPA (1991f, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

A chronic oral exposure limit of 5 µg/kg bw/d was developed by the U.S. EPA (1991f, Website) based on a NOAEL of 0.015 mg/kg bw/d for clinical selenosis observed in a human epidemiological study of 400 individuals from China. The lowest whole blood selenium concentration of 1.0 mg/L, at which no effects were observed, corresponded to a NOAEL of 0.85 mg/d. The U.S. EPA (1991f, Website) applied an uncertainty factor of 3 to the NOAEL to account for sensitive individuals. An uncertainty factor of 3 (rather than 10) was considered appropriate as similar NOAELs were identified in two other moderately-sized populations exposed to excess selenium throughout their lifetime (U.S. EPA 1991f, Website). The oral RfD of 5 µg/kg bw/d was used in the chronic effects assessment for selenium.

The ATSDR (2003, 2006a) also recommends a chronic oral exposure limit of 5.0 µg/kg bw/d based on the same study and NOAEL as the U.S. EPA. Similarly, the ATSDR applied an uncertainty factor of 3 to the NOAEL of 0.015 mg/kg bw/d to account for human variability.

An inhalation bioavailability of 100% (assumed), oral bioavailability of 44% (RAIS 2007, Website) and dermal bioavailability of 0.1% (RAIS 2007, Website) were assumed for incorporation in the multiple exposure pathway model.

3.34 SULPHUR DIOXIDE

Chemicals of potential concern that are governed and defined at the federal government level in the form of either National Ambient Air Quality Objectives (NAAQOs) or as a Canada-Wide Standard (CWS) were not subjected to the typical screening process. Instead, the AAQOs adopted by the AENV (2007, Website) from Health Canada were given priority. Sulphur dioxide is one of these chemicals.

3.34.1 Acute Exposure Limit

The acute exposure limits used for the assessment of sulphur dioxide concentrations in air were based primarily on AENV's (2007, Website) AAQOs. These include a 1-hour objective of 450 µg/m^3 and a 24-hour objective of 150 µg/m^3. These AAQOs were adopted from the Health Canada NAAQOs, which recommends maximum desirable, acceptable and tolerable objectives for sulphur dioxide. The Alberta objectives are based on the maximum desirable levels (i.e., the lowest objective). These guidelines are health-based and rely on controlled studies of the most sensitive population (i.e., asthmatics) to air pollutants such as sulphur dioxide.

Sulphur dioxide also was assessed using a 10-minute air quality guideline of 500 µg/m^3 developed by the WHO (2000, Website). This guideline is based on changes in lung function in asthmatics (WHO 2000, Website).

Using the above objectives and guidelines, the acute assessment for sulphur dioxide was completed on a 10-minute, 1-hour and 24-hour basis.

3.34.2 Chronic Exposure Limit(s)

The chronic exposure limit used for the assessment of sulphur dioxide concentrations in air was based on AENV's (2007, Website) annual ambient air quality objective for sulphur dioxide of 30 µg/m^3. This AAQO was adopted from the Health Canada annual NAAQO, which includes maximum desirable, acceptable and tolerable objectives for sulphur dioxide. The Alberta objectives are based on the maximum desirable levels (i.e., the lowest objective). This guideline is health-based and relies on controlled studies of the most sensitive population (i.e., asthmatics) to air pollutants such as sulphur dioxide.

Sulphur dioxide was assessed only on an inhalation exposure basis because potential health effects relate directly to inhalation exposure.

3.35 TOLUENE

3.35.1 Acute Exposure Limit

Table 76 shows the acute inhalation exposure limits for toluene as defined by the regulatory agencies.

Table 76 Acute Inhalation Exposure Limits for Toluene

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	1,880 400	1-hour 24-hour	AENV (2007, Website)
ATSDR	3,800	24-hour	ATSDR (2006a)
OEHHA	37,000	1-hour	OEHHA (2007a)
OMOE	2,000	half-hour, 24-hour	OMOE (2005a)
WHO	260	1-week	WHO (2000, Website)

The AENV (2007, Website) provides a 1-hour AAQO of 1,880 µg/m^3, which was adopted from the TCEQ. In turn the TCEQ ESL was based on the ACGIH TLV-TWA of 50 ppm (188 mg/m^3) for altered CNS performance (TCEQ 2003, Website; ACGIH 1991, 2006a). The AENV (2007, Website) adjusted the TLV-TWA by applying a 100-fold uncertainty factor. The basis of this 100-fold uncertainty factor is unknown. As well, TLV-TWAs are developed to be protective of a worker repeatedly exposed during an eight-hour workday and a 40-hour workweek. Because the study team does not support the use of chronic toxicity data in the derivation of an acute limit, this 1-hour AAQO was not used in the acute health effects assessment.

The 24-hour AAQO of 400 µg/m^3 was adopted from the Michigan Department of Environmental Quality and the Washington Department of Ecology (AENV 2007, Website). These regulatory agencies based their 24-hour guidelines on the U.S. EPA (AENV 2004b) chronic inhalation RfC of 400 µg/m^3. The U.S. EPA (2005d, Website) RfC has since been revised to an inhalation RfC of 5,000 µg/m^3 for neurological effects. The study team does not support the use of chronic toxicity data in the derivation of an acute limit and thus did not use this 24-hour AAQO in the acute health effects assessment.

The OMOE (2005a) has developed a 24-hour AAQC of 2,000 µg/m^3 for toluene based on odour perception and thus was not used in the acute health effects assessment.

The WHO (2000, Website) provides a guideline of 260 ug/m^3 based on a 1-week averaging time. A LOAEL of 332 mg/m^3 (88 ppm) was identified for CNS effects from occupational studies. The LOAEL was adjusted for continuous exposure (8 hour/24 hour x 5 days/7 days) to a concentration of 79 mg/m^3. The WHO (2000, Website) applied an uncertainty factor of 300 to the duration-adjusted LOAEL to account for intra-species variability (10-fold), use of a LOAEL (10-fold) and for the given effects on the developing CNS (3-fold). This guideline was not used in the short-term assessment of toluene as the

ATSDR (2006a) and OEHHA (2007a) both provide acute exposure limits based on a NOAEL.

The ATSDR (2000c, 2006a) has derived an acute MRL of 1 ppm (3,800 µg/m^3) for neurological effects. A NOAEL of 40 ppm (150 mg/m^3) was reported based on a study by Andersen et al. (1983), wherein 16 healthy young subjects with no previous exposure to organic solvents were exposed to toluene for six hours per day on four consecutive days. The ATSDR (2000c) adjusted the NOAEL for intermittent exposure (8 hours/24 hours x 5 days/7 days). A 10-fold uncertainty factor was applied to the duration-adjusted NOAEL to account for intra-species variability (ATSDR 2000c). The adjustment from 6-hour exposure to a 24-hour limit using 8 hours/24 hours x 5 days/7 days is a common approach for deriving a chronic limit from intermittent occupational exposure of eight hours per day, five days per week; however, this adjustment is inappropriate when deriving a 24-hour limit from 6-hour exposure.

The OEHHA (1999i, 2007a) provides an acute REL of 37,000 µg/m^3 for toluene based on the same NOAEL of 40 ppm (150 mg/m^3) identified in the ATSDR assessment. The discrepancy between the limit values of the OEHHA and the ATSDR arises from the extrapolation of a 1-hour and 24-hour limit value, respectively. The OEHHA (1999i) converted the 6-hour exposure duration to a 1-hour REL of 98 ppm (370 mg/m^3) based on a modified Haber's Law:

$$C_{ADJ}^{n} \times T_{ADJ} = C^{n} \times T$$

$$C^{2} \times 1 \text{ hour} = (40 \text{ ppm})^{2} \times 6 \text{ hours}$$

Where:

C_{ADJ} = duration-adjusted concentration

T_{ADJ} = desired time of exposure (1 hour)

C = concentration of exposure (40 ppm)

T = time of exposure (6 hours)

n = chemical-specific modification factor designed to account for the toxicity of a chemical being concentration and/or duration dependent. The OEHHA (1999a) recommends using a default *n* value of 2 in the adjustment for greater than 1-hour exposure.

The same uncertainty factor of 10 for intra-species variability was then applied by the OEHHA (1999i) to the duration-adjusted NOAEL, resulting in acute REL of 37,000 µg/m^3.

The ATSDR and the OEHHA share the opinion that a NOAEL of 150 mg/m^3 is appropriate for short-term inhalation of toluene and that an uncertainty factor of 10 is sufficiently protective of the general population. However, the OEHHA's adjustment for exposure using Haber's Law is more appropriate and thus the acute REL of 37,000 µg/m^3 was used as a 1-hour exposure limit in the acute effects assessment of toluene.

3.35.2 Chronic Exposure Limit(s)

Table 77 shows the chronic inhalation exposure limits for toluene as defined by the regulatory agencies.

Table 77 Chronic Inhalation Exposure Limits for Toluene

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	300	RfC	ATSDR (2006a)
Health Canada	3,800	RfC	Health Canada (2004b)
RIVM	400	RfC	RIVM (2001)
U.S. EPA	5,000	RfC	U.S. EPA (2005d, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

The ATSDR (2000c, 2006a) chronic inhalation MRL of 0.08 ppm (300 µg/m^3) was based on colour vision impairment in workers exposed to toluene. Three groups of Croatian workers were examined through interviews, medical examinations and colour vision testing (ATSDR 2000c; Zavalic et al. 1998). A LOAEL of 35 ppm (130 mg/m^3) was determined for alcohol- and age-adjusted colour vision impairment. The LOAEL was adjusted for intermittent exposure (8 hours/24 hours x 5 days/7 days) to a concentration of 8 ppm (30 mg/m^3). The ATSDR (2000c) applied an uncertainty factor of 100 to the duration-adjusted LOAEL to account for intra-species variability (10-fold) and use of a LOAEL (10-fold). This MRL was not used as the chronic exposure limit for toluene because it was developed from a LOAEL and thus required the use of a 10-fold uncertainty factor acknowledging the uncertainty associated with use of a LOAEL instead of a NOAEL. As such, the RfCs developed by Health Canada and the U.S. EPA from NOAELs were given preference.

The RIVM has developed a TCA of 400 µg/m^3 for toluene (RIVM 2001). This TCA was adopted from the U.S. EPA (2005d, Website), which revised its RfC in 2005 to a value of 5,000 µg/m^3. As a result, this TCA was not used in the chronic inhalation effects assessment for toluene.

Health Canada bases its chronic tolerable concentration of 3,800 µg/m^3 on the same lowest reported NOAEL of 150 mg/m^3 (40 ppm) for neurological effects and respiratory irritation in human volunteers as used by the ATSDR to derive the acute MRL (Andersen et al. 1983; CEPA 1992). The study NOAEL was adjusted from 6-hour daily dosing to continuous exposure and an uncertainty factor of 10 was applied to account for intra-species variability.

The U.S. EPA (2005d, Website) has derived an inhalation RfC based upon the findings of 10 human studies, each of which examined the neurological effects in occupationally exposed workers. These studies were all more recent than the Andersen et al. (1983) study used in the Health Canada assessment and included the study used as the basis of the ATSDR chronic MRL. The analysis of the multiple studies resulted in an average NOAEL of 34 ppm (128 mg/m^3). This NOAEL was adjusted for the differences in breathing rates between workers and members of the public and the reduced weekly exposure time (U.S. EPA 2005d, Website):

$$NOAEL_{ADJ} = NOAEL \times \frac{10\ m^3/d}{20\ m^3/d} \times \frac{5\ days}{7\ days}$$

The U.S. EPA (2005d, Website) also applied an uncertainty factor of 10 to the $NOAEL_{ADJ}$ to account for human variation. The U.S. EPA RfC of 5,000 µg/m^3 represents the most recent analysis of the available scientific literature and therefore was used in the current assessment.

Toluene was not incorporated into the multiple pathway exposure assessment since it did not exceed any of the persistence and bioaccumulation parameters established by Environment Canada (2008, Website). Thus, a chronic oral limit was not required for toluene.

3.36 TRIMETHYLBENZENES

3.36.1 Acute Exposure Limits

Table 78 shows the acute inhalation exposure limits for trimethylbenzenes as defined by the regulatory agencies.

Table 78 Acute Inhalation Exposure Limits for Trimethylbenzenes

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	—	—	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	—	—	OEHHA (2007a)
OMOE	1,000	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The OMOE (2005a, 2006d) provides a 24-hour standard for 1,2,4-trimethylbenzene based on odour and health considerations. However, the OMOE (2006d) recently proposed a 24-hour standard of 300 µg/m^3 for trimethylbenzenes based on CNS effects. Several subchronic rat studies demonstrated CNS effects associated with inhalation exposure to trimethylbenzenes. In all five supporting studies, rats were exposed to toluene vapours for six hours per day, five days per week. For 1,23-trimethylbenzene, CNS effects were reported at 123 and 492 mg/m^3. CNS effects were reported for 1,3,5-trimethylbenzene and 1,2,4-trimethylbenzene at 492 mg/m^3. The OMOE (2006d) concluded that long-term CNS effects following 4 weeks of inhalation exposure may occur at concentrations as low as 492 mg/m^3. This value was identified as the LOAEL and the OMOE (2006d) adjusted the LOAEL to continuous exposure (6 hours/24 hours x 5 days/7 days).

The OMOE (2006d) applied an uncertainty factor of 300 to the duration-adjusted LOAEL to account for interspecies variability (3-fold), intra-species variability (10-fold), extrapolation from a LOAEL to a NOAEL (3-fold) and extrapolation from subchronic to chronic exposure (3-fold). An uncertainty factor of 3 was considered sufficient for extrapolating from a LOAEL to a NOAEL because the observed effects were not considered severe (OMOE 2006d). Animal and human toxicity demonstrate that trimethylbenzene and different trimethylbenzene isomers produce similar effects around the same exposure concentrations, thus a factor of 3 was considered appropriate for interspecies extrapolations (OMOE 2006d).

Derivation of an acute standard from a subchronic LOAEL is a conservative approach since a higher exposure over a shorter time-period (i.e., acute exposure) presumably could occur without risk of adverse effects. The neurotoxic effects associated with trimethylbenzene could feasibly occur in association with a relatively short exposure period, thus the exposure limit is considered relevant. Consequently, adjusting for discontinuous exposure (6 hours/24 hours x 5 days/7 days) and use of a 3-fold uncertainty factor to account for "extrapolating from subchronic to chronic exposure" is unnecessary (and inappropriate). Removal of the duration adjustment and uncertainty factor results in an acute standard of 5,000 µg/m^3. Although the study team does not support the use of subchronic toxicity data in the derivation of an acute limit, an alternate guideline based on acute toxicity data is not available. Thus, the adjusted 6-hour standard of 5,000 µg/m^3 was conservatively used in the acute effects assessment as a 1-hour exposure limit.

3.36.2 Chronic Exposure Limit(s)

Table 79 shows the chronic inhalation exposure limits for trimethylbenzenes as defined by the regulatory agencies

Table 79 Chronic Inhalation Exposure Limits for Trimethylbenzenes

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	—	—	RIVM (2001)
U.S. EPA	—	—	U.S. EPA (2007, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

A chronic inhalation exposure limit has not been established by any of the above regulatory agencies for trimethylbenzenes. Thus, the toxicity search was expanded to include chronic RELs provided by the OEHHA (2007b) and long-term occupational limit values (i.e., TLV-TWAs; ACGIH 2006a).

The ACGIH (1991, 2006a) provides a TLV-TWA for trimethylbenzene (all isomers) of 25 ppm (123 mg/m^3) based on CNS effects and respiratory irritation. Workers exposed to a mixture of trimethylbenzenes at up to 60 ppm reported CNS changes, asthmatic bronchitis and blood dyscrasis. However, the blood abnormalities were attributed to contamination from benzene (ACGIH 1991). Exposure to 35 to 50 ppm caused no complaints of mucous membrane irritation (ACGIH 1991). The TLV-TWA is considered to be protective of a worker repeatedly exposed during an 8-hour workday and a 40-hour workweek

(ACGIH 2006a). The TLV-TWA was adjusted from an 8-hour time-weighted average occupational exposure to continuous exposure using the following calculation (U.S. EPA 2002):

$$\text{TLV-TWA}_{ADJ} = \text{TLV-TWA} \times \frac{MV_{ho}}{MV_h} \times \frac{Exp_{ho}}{Exp_h}$$

Where:

TLV-TWA_{ADJ} = chemical-specific TLV-TWA for chronic exposure via inhalation (mg/m^3)

TLV-TWA = chemical-specific TLV-TWA (123 mg/m^3)

MV_{ho} = amount of air used by a worker during an 8-hour work period (10 m^3/d)

MV_h = amount of air used by an individual in the general population during a day (20 m^3/d)

Exp_{ho} = days per week a worker is exposed (5 days)

Exp_h = days per week an individual in the general population is exposed (7 days)

An uncertainty factor of 10 was applied to the TLV-TWA_{ADJ} of 44 mg/m^3 to account for intra-species variability, resulting in a modified chronic inhalation limit of 4,400 $\mu g/m^3$. This modified limit was used in the chronic inhalation effects assessment of trimethylbenzenes.

Trimethylbenzenes were not incorporated into the multiple pathway exposure assessment since it did not exceed the persistence and bioaccumulation parameters established by Environment Canada (2008, Website). As a result, a chronic oral exposure limit was not required for trimethylbenzenes.

3.37 VANADIUM

3.37.1 Acute Exposure Limit

Table 80 shows the acute inhalation exposure limits for vanadium as defined by the regulatory agencies.

Table 80 Acute Inhalation Exposure Limits for Vanadium

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	—	—	AENV (2007, Website)
ATSDR	0.2[(a)]	24-hour	ATSDR (2006a)
OEHHA	30[(a)]	1-hour	OEHHA (2007a)
OMOE	2	24-hour	OMOE (2005a)
WHO	1	24-hour	WHO (2000, Website)

[(a)] Exposure limit based on vanadium pentoxide.

— = Not available.

The ATSDR (1992, 2006a) provides an acute inhalation MRL of 0.2 µg/m^3 based on bronchial irritation in human volunteers exposed for eight hours to vanadium pentoxide. Nine male volunteers were exposed to 0.1, 0.25 or 1.0 mg/m^3 vanadium pentoxide for eight hours (Zenz and Berg 1967). A LOAEL of 0.06 mg of vanadium/m^3 was identified based on irritation in two of the volunteers and adjusted to a full day exposure (8 hours/24 hours). The ATSDR (1992) applied an uncertainty factor of 100 to the duration-adjusted NOAEL to account for intra-species variability and use of a LOAEL.

The OEHHA (1999j, 2007a) used the same inhalation study as the ATSDR in the derivation of an acute REL of 30 µg/m^3 for vanadium pentoxide. A LOAEL of 0.25 mg/m^3 for vanadium pentoxide was identified in five of the human volunteers and a LOAEL of 0.1 mg/m^3 was identified in two of the volunteers (OEHHA 1999j). The critical effect was identified as subjective reports of increased respiratory mucous production that was cleared by coughing. The OEHHA (1999j) adjusted the LOAEL of 0.1 mg/m^3 from an 8-hour exposure to a 1-hour exposure using a modified Haber's Law (OEHHA 1999a):

$$C_{ADJ}^{n} \times T_{ADJ} = C^{n} \times T$$

$$C^{2} \times 1 \text{ hour} = (0.1 \text{ mg/m}^3)^2 \times 8 \text{ hours}$$

Where:

C_{ADJ} = duration-adjusted concentration

T_{ADJ} = desired time of exposure (1 hour)

C = concentration of exposure (0.1 mg/m^3)

T = time of exposure (8 hours)

n = chemical-specific modification factor designed to account for the toxicity of a chemical being concentration and/or duration dependent. The OEHHA (1999a) recommends using a default *n* value of 2 in the adjustment for greater than 1-hour exposure.

The OEHHA (1999j) applied an uncertainty factor of 10 to the duration-adjusted LOAEL to account for intra-species variability. An uncertainty factor of 1 was applied for the use of a LOAEL because the effects observed were not adverse (OEHHA 1999j).

Although the OEHHA and ATSDR selected the same study to derive their inhalation exposure limits. The OEHHA (1999j) acute REL is for vanadium pentoxide; whereas, the ATSDR (1992) calculated a limit for vanadium. Thus, the MRL of 0.2 µg/m^3 for a 24-hour exposure was used in the acute effects assessment of vanadium.

3.37.2 Chronic Exposure Limit(s)

Table 81 shows the chronic inhalation exposure limits for vanadium as defined by the regulatory agencies.

Table 81 Chronic Inhalation Exposure Limits for Vanadium

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	—	—	RIVM (2001)
U.S. EPA	—	—	U.S. EPA (2007, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

A chronic inhalation exposure limit has not been established by any of the above regulatory agencies for vanadium. However, the WHO (2000, Website) has recommended a 24-hour limit of 1 µg/m^3 based on a LOAEL of 20 µg/m^3 for chronic upper respiratory tract irritation. The chronic LOAEL identified by the WHO (2000, Website) is based on an occupational study. Thus, the study team adjusted the LOAEL from an eight-hour time weighted average for occupational exposure to a value of 7 µg/m^3 for continuous exposure in the general population as follows:

$$LOAEL_{ADJ} = LOAEL \times \frac{MV_{ho}}{MV_h} \times \frac{Exp_{ho}}{Exp_h}$$

Where:

$LOAEL_{ADJ}$ = lowest-observed-adverse-effect-level in the human population from continuous exposure (mg/m^3)

LOAEL = lowest-observed-adverse-effect-level for discontinuous exposure in an occupational setting (0.02 mg/m^3)

MV_{ho} = amount of air used by a worker during an 8-hour work period (10 m^3/d)

MV_h = amount of air used by an individual in the general population during a day (20 m^3/d)

Exp_{ho} = days per week a worker is exposed (5 days)

Exp_h = days per week an individual in the general population is exposed (7 days)

An uncertainty factor of 100 was applied to the $LOAEL_{ADJ}$ value to account for intra-species variability (10-fold) and use of a LOAEL (10-fold), resulting in a chronic RfC of 0.07 $\mu g/m^3$. As no other inhalation criteria or guidelines were identified by the other regulatory agencies, the modified limit of 0.07 $\mu g/m^3$ was used in the chronic effects assessment for vanadium. The RfC equates to an inhaled dose of 0.016 µg/kg bw/d based on an adult body weight of 70.7 kg and inhalation rate of 15.8 m^3/day (Health Canada 2004a).

Given that vanadium could persist or bioaccumulate in the environment, an oral exposure limit was required (Table 82).

Table 82 Chronic Oral Exposure Limits for Vanadium

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	—	—	RIVM (2001)
U.S. EPA	9[(a)]	RfD	U.S. EPA (1996c, Website)
WHO	—	—	WHO (2000, Website)

[(a)] Exposure limit based on vanadium pentoxide.

— = Not available.

The U.S. EPA (1996c, Website) recommends an oral RfD of 9 µg/kg bw/d based on decreased hair cystine in a chronic oral study. Rats were administered 10 or 100 ppm vanadium (17.9 or 179 ppm vanadium pentoxide) in the diet for 2.5 years. A NOAEL of 17.9 ppm was identified and converted to a dose of 0.89 mg/kg/d assuming a rat eats food equivalent to 5% of their body weight. The U.S. EPA (1996c, Website) applied an uncertainty factor of 100 to account for interspecies variability (10-fold) and intra-species variability (10-fold). However, to derive an exposure limit for vanadium, it is more appropriate to use the dietary level of 10 ppm vanadium (the COPC of interest) rather than only evaluating the fraction that is vanadium pentoxide (the compound upon which the U.S. EPA value is based). Assuming the adult rat food consumption of 5% body weight per day, a NOAEL of 0.5 mg/kg bw/d for vanadium can be calculated. Application of the U.S. EPA (1996c, Website) uncertainty factor of 100, results in a modified oral exposure limit of 5 µg/kg bw/d for vanadium. The RfD of 5 µg/kg bw/d was used in the chronic assessment of vanadium.

For the multiple exposure pathway model, an inhalation bioavailability of 100% was assumed and an oral bioavailability of 1% and dermal bioavailability of 0.1% were applied (RAIS 2007, Website).

3.38 XYLENES

3.38.1 Acute Exposure Limit

Table 83 shows the acute inhalation exposure limits for xylenes as defined by the regulatory agencies.

Table 83 Acute Inhalation Exposure Limits for Xylenes

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	2,300 700	1-hour 24-hour	AENV (2007, Website)
ATSDR	8,700	2-hour	ATSDR (2006a)
OEHHA	22,000	1-hour	OEHHA (2007a)
OMOE	730	24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The AENV (2007, Website) adopted the OMOE's half-hour point-of-impingement of 2,300 µg/m^3 as its 1-hour AAQO. However, this POI was based on odour perception and has since been updated (OMOE 2005a). The AENV (2007, Website) also provides a 24-hour AAQO of 700 µg/m^3. This guideline

was not used in the acute effects assessment because it was taken from the chronic REL provided by the OEHHA (2007a).

The OMOE (2005a,c) currently provides a 24-hour limit of 730 µg/m^3 based on adverse neurological effects. A LOAEL of 62 mg/m^3 was established for headaches, eye and nasal irritation and light headedness (floating sensation) in approximately 300 workers, 175 of whom were occupationally exposed for an average of seven years. The LOAEL was adjusted by the OMOE (2005c) to account for discontinuous exposure to a concentration of 22.1 mg/m^3:

$$LOAEL_{ADJ} = LOAEL \times \frac{10\ m^3/d}{20\ m^3/d} \times \frac{5\ days}{7\ days}$$

It should be noted that the scientific merit for the discontinuous exposure adjustment is questionable, considering that the OMOE standard is intended to be protective of short-term exposures and that the study subjects were exposed to xylene on average for seven years. Regardless, the OMOE (2005c) applied an uncertainty factor of 30 to the adjusted LOAEL to account for intra-species variability (10-fold) and use of a LOAEL (3-fold).

The ATSDR (2005d, 2006a) recently reviewed the short-term toxicity of xylenes. Based on a study by Ernstgard et al. (2002), 50 ppm (200 mg/m^3) was designated as a LOAEL for slight respiratory effects (e.g., reduced forced vital capacity, increased discomfort in throat and airways in women and breathing difficulties in both sexes) and subjective symptoms of neurotoxicity (e.g., headache, dizziness, feelings of intoxication). Fifty-six healthy volunteers (28 per sex) between the ages of 20 and 49 years were exposed to 50 ppm m-xylene, clean air (controls) or 150 ppm 2-propanol in a dynamic chamber for two hours (Ernstgard et al. 2002). Each subject received three treatments separated by intervals of two weeks. The LOAEL was considered minimal because the magnitude of the changes was small (ATSDR 2005d). The ATSDR (2005d) applied an uncertainty factor of 30 for intra-species variability (10-fold) and use of a (minimal) LOAEL (3-fold), resulting in an acute MRL of 2 ppm (8,700 µg/m^3). This 2-hour MRL of 8,700 µg/m^3 was conservatively adopted as the 1-hour exposure limit used in the acute effects assessment.

3.38.2 Chronic Exposure Limit(s)

Table 84 shows the chronic inhalation exposure limits for xylenes as defined by the regulatory agencies.

Table 84 Chronic Inhalation Exposure Limits for Xylenes

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	650	RfC	ATSDR (2006a)
Health Canada	180	RfC	Health Canada (2004b)
RIVM	870	RfC	RIVM (2001)
U.S. EPA	100	RfC	U.S. EPA (2003c, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

Although Health Canada (2004b) recommends a tolerable concentration of 180 µg/m^3 for xylenes, the specific basis is unknown. Therefore, the chronic inhalation RfC derived by the U.S. EPA (2003c, Website) of 100 µg/m^3 was used in the chronic effects assessment. The RfC was derived from a NOAEL of 217 mg/m^3 for impaired motor coordination from a subchronic inhalation study in male rats (Korsak et al. 1994). The NOAEL was adjusted from intermittent to continuous exposure by the U.S. EPA (2003c, Website), resulting in an adjusted NOAEL of 39 mg/m^3. A safety factor of 300 was applied by the U.S. EPA (2003c, Website) to the adjusted NOAEL to account for laboratory animal-to-human interspecies differences (3-fold), intra-species uncertainty to account for human variability and sensitive populations (10-fold), extrapolation from subchronic to chronic duration (3-fold) and uncertainties in the database (3-fold). The U.S. EPA RfC of 100 µg/m^3 was selected as the chronic inhalation limit for xylenes.

Xylenes were not incorporated into the multiple pathway exposure assessment since it did not exceed any of the persistence and bioaccumulation parameters established by Environment Canada (2008, Website). Thus, a chronic oral limit was not required for xylenes.

3.39 ZINC

3.39.1 Acute Exposure Limit

Table 85 shows the acute inhalation exposure limits for zinc as defined by the regulatory agencies.

Table 85 Acute Inhalation Exposure Limits for Zinc

Regulatory Agency	Value [µg/m^3]	Averaging Time	Source
AENV	—	—	AENV (2007, Website)
ATSDR	—	—	ATSDR (2006a)
OEHHA	—	—	OEHHA (2007a)
OMOE	Zinc: 120 Zinc chloride: 10 Zinc stearate: 35	24-hour 1-hour 24-hour	OMOE (2005a)
WHO	—	—	WHO (2000, Website)

— = Not available.

The OMOE (2005a) has developed several inhalation criteria for zinc; however, there is no available supporting documentation for these values. As a result, the study team is unable to comment on the scientific merit of these limits and did not use them in the acute effects assessment of zinc.

There are no acute inhalation criteria or guidelines provided by any of the other regulatory agencies. Consequently, the toxicity search was expanded to include intermediate MRLs provided by the ATSDR (2006a) and occupational short-term exposure values (i.e., STEL, Ceiling) provided by the ACGIH (2006a).

The ACGIH (1991, 2006a) provides a TLV-STEL of 2 mg/m^3 for zinc chloride (fume) to minimize the potential for respiratory irritation and pulmonary function. Mild, transient respiratory irritation was identified following 30-minute exposure to 4.8 mg/m^3 and no effects were associated with a concentration of 0.4 mg/m^3 (ACGIH 1991). In addition, the ACGIH (1991, 2006a) also provides a TLV-STEL of 10 mg/m^3 for zinc oxide (fume) based on the incidence of metal fume fever. As fumes are not the relevant form of zinc to this assessment, neither one of these limits was employed in the assessment. As no defensible acute exposure limit was available, zinc was not evaluated on an acute basis. As a result, zinc was assessed on a chronic basis only.

3.39.2 Chronic Exposure Limit(s)

Table 86 shows the chronic inhalation exposure limits for zinc as defined by the regulatory agencies.

Table 86 Chronic Inhalation Exposure Limits for Zinc

Regulatory Agency	Value [µg/m^3]	Type	Source
ATSDR	—	—	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	—	—	RIVM (2001)
U.S. EPA	—	—	U.S. EPA (2005e, Website)
WHO	—	—	WHO (2000, Website)

— = Not available.

Chronic inhalation criteria or guidelines for zinc are not available from the above regulatory agencies. Consequently, the toxicity search was expanded to chronic RELs by the OEHHA (2007b) and occupational exposure limits by the ACGIH (2006a).

The ACGIH (1991, 2006a) provides a TLV-TWA of 0.01 mg/m^3 protective of cancer for zinc chromates based on evidence from epidemiological studies. However, these epidemiological studies included mixed exposures of zinc chromates and lead chromates; therefore, it is difficult to separate the effects due to zinc chromates from those due to lead chromates (ACGIH 1991, 2006a). Further, the U.S. EPA (2005e, Website) considers the evidence of possible carcinogenicity of zinc from human occupational exposure studies to be inadequate or inconclusive.

The ACGIH (1991, 2006a) also provides a TLV-TWA of 1 mg/m^3 for zinc chloride fume, 2 mg/m^3 for zinc oxide fume and 2 mg/m^3 for zinc oxide dusts. As metal fumes may not be the most relevant form of zinc for the purposes of this assessment, the TLV-TWA for dusts was selected. The TLV-TWA of 2 mg/m^3 for zinc oxide dusts based on respiratory effects is considered to be protective of a worker repeatedly exposed during an 8-hour workday and a 40-hour workweek (ACGIH 1991, 2006a). The TLV–TWA was adjusted from an 8-hour time-weighted average occupational exposure to continuous exposure using the following calculation (U.S. EPA 2002):

$$\text{TLV-TWA}_{ADJ} = \text{TLV-TWA} \times \frac{MV_{ho}}{MV_h} \times \frac{Exp_{ho}}{Exp_h}$$

Where:

TLV-TWA_{ADJ} = chemical-specific TLV-TWA for chronic exposure via inhalation (mg/m^3)

TLV-TWA = chemical-specific TLV-TWA (2 mg/m^3)

MV_{ho} = amount of air used by a worker during an 8-hour work period (10 m^3/d)

MV_h = amount of air used by an individual in the general population during a day (20 m^3/d)

Exp_{ho} = days per week a worker is exposed (5 days)

Exp_h = days per week an individual in the general population is exposed (7 days)

An uncertainty factor of 10 was applied to the TLV–TWA_{ADJ} of 0.7 mg/m^3 to account for intra-species variability, resulting in a modified chronic inhalation exposure limit of 70 µg/m^3. The chronic inhalation exposure limit of 70 µg/m^3 was used in the chronic effects assessment and is equivalent to a dose of 16 µg/kg bw/day, assuming an adult body weight of 70.7 kg and an adult inhalation rate of 15.8 m^3/day (Health Canada 2004a).

Given that zinc could persist or bioaccumulate in the environment, an oral exposure limit was required (Table 87).

Table 87 Chronic Oral Exposure Limits for Zinc

Regulatory Agency	Value [µg/kg bw/d]	Type	Source
ATSDR	300	RfD	ATSDR (2006a)
Health Canada	—	—	Health Canada (2004b,c)
RIVM	500	RfD	RIVM (2001)
U.S. EPA	300	RfD	U.S. EPA (2005e, Website)
WHO	1,000	RfD	WHO (2003c)

— = Not available.

The U.S. EPA (2005e, Website) provides an oral exposure limit of 300 µg/kg bw/d based on decreases in erythrocyte copper, zinc-superoxidase dismutase (ESOD) activity. A LOAEL of 0.91 mg/kg bw/d was derived as an average from effect levels reported in four separate studies conducted in male and female volunteers: 0.81 mg/kg bw/d, 0.94 mg/kg bw/d and 0.99 mg/kg bw/d (U.S. EPA 2005e, Website). The average daily intakes were added to the reported supplemental doses to determine the total doses, which were then adjusted by body weight to derive the effect levels. The U.S. EPA (2005e, Website) applied an uncertainty factor of 3 to account for intra-species variability. An uncertainty factor to account for extrapolation from a subchronic study to a chronic exposure limit was deemed unnecessary as zinc is an essential nutrient and thus chronic exposure is required for proper nutrition (U.S. EPA 2005e, Website). Further, the RfD is expected to be without adverse effects when consumed on a daily

basis over a lifespan (U.S. EPA 2005e, Website). An uncertainty factor for use of a LOAEL was not incorporated as the RfD is based on a minimal effect level for a sensitive biological indicator (U.S. EPA 2005e, Website). Finally, the U.S. EPA (2005e, Website) did not apply an uncertainty factor greater than 3 for intra-species variability as this would result in an exposure limit lower than the daily requirement for sensitive humans. The oral RfD of 300 µg/kg bw/d was used in the current chronic effects assessment.

The ATSDR (2005e, 2006a) also recommends a chronic oral MRL of 300 µg/kg bw/d, which was adopted from their intermediate oral MRL. The intermediate MRL is also based on decreases in ESOD activity, as well as on changes in serum ferritin in women. This study was included as one of the principal studies in the U.S. EPA's assessment of zinc. However, the ATSDR (2005e) identified the supplemental dose of 0.83 mg/kg bw/d as a NOAEL, rather than a LOAEL. Although effects were observed at the supplemental dose of 0.83 mg/kg bw/d, the ATSDR (2005e) considered these effects to be a precursor event to more severe symptoms, rather than a toxic effect itself. Further, the ATSDR (2005e) did not add the average daily dose of zinc to the supplemental dose to determine a total dose, as the U.S. EPA did. Similar to the U.S. EPA, the ATSDR (2005e) applied an uncertainty factor of 3 to account for human variability.

An inhalation bioavailability of 100% (assumed), oral bioavailability of 20% (RAIS 2007, Website) and dermal bioavailability of 0.1% (RAIS 2007, Website) were assumed for incorporation in the multiple exposure pathway model.

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